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ARCHIVES OF SURGERY

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AIR EMBOLISM FROM THE PULMONARY VEIN

A CLINICAL AND EXPERIMENTAL STUDY *

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Air embolism, with the pulmonary vein as the portal of entry, may complicate nearly any surgical procedure on the lung. Graham [1] experienced two fatalities from this source in forty-five operations of cautery pneumectomy, and it has occurred in as simple a procedure as irrigation of an empyema cavity. Brauer [2] termed the condition arterial air embolism and emphasized its frequence as a complication of artificial pneumothorax. While the cause of the syncope, collapse and death that are occasionally seen during pneumothorax induction is not always clear, it is doubtless often air embolism. Stivelman [3] reported seven instances occurring in 162 primary punctures; Forlanini [4] had twelve in 134, and Sachs [5] collected twenty-two in 1,122 from the literature.

Sharp distinction must be made at once between this form of air embolism and that in which air enters a peripheral vein, as the jugular or subclavian. In the former, air enters the peripheral arteries and may involve every organ and tissue, while in the latter air passes into the pulmonary arteries and exerts its effects on the lesser circulation and right side of the heart.

In this article are presented certain clinical and experimental data and deductions concerning air embolism from the pulmonary vein. A brief summary of current knowledge is given to introduce each phase

* Submitted for publication, May 13, 1929.

1. Graham, E. A.: Ann. Surg. **86**:174, 1927.

2. Brauer, L. D.: Ztschr. f. Nervenh. **45**:276, 1912. Brauer, L.; Schröder, G., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, J. A. Bath, 1923, vol. 2, p. 461.

3. Stivelman, B. P.: Am. J. M. Sc. **165**:836, 1923.

4. Forlanini, C.: Ergebn. d. inn. Med. u. Kinderh. **9**:621, 1912.

5. Sachs, T. B.: Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis, J. A. M. A. **65**:1861 (Nov. 27) 1915.

of the subject. Complete reviews of the literature are available elsewhere.[6]

ETIOLOGY

Air may enter the pulmonary vein spontaneously or may be injected.

The venous pressure in the pulmonary circulation is ordinarily less than that of the atmosphere, and should the lumen of a vein be freely opened air is drawn into the blood stream. This has occurred in such operations as pneumectomy, pneumotomy, pulmonary decortication, dissection or probing within the lung and separation of the pleural adhesions. Injection of air or other gases directly or indirectly into the circulation has occurred in the production of artificial pneumothorax. The needle may accidentally enter the lung and one of its vessels, or when the puncture has been accurate and the gas enters the pleural cavity an adhesion between the lung and the wall of the chest may tear and open a pulmonary vein. Air from the pleural cavity may then enter the torn vessel.

Essentially the same type of embolism has been known to arise in other ways: Air that has entered a peripheral vein and has been carried to the right side of the heart occasionally finds its way through a patent foramen ovale into the left auricle.[7] That the foramen ovale is frequently patent without evidence during life is well known. Herxheimer [8] found from 20 to 50 per cent patent during routine examination at autopsy; Otto [9] noted 286 in 1,130 consecutive autopsies in Dresden material, of which 200 admitted a probe only and eighty-six were of comparatively large size; Lubarsch [10] found patency in 25 per cent, and Kaufmann [11] in 32.5 per cent.

In 1808, Bichat [12] demonstrated that when air is blown into the lungs of a living animal at a pressure no greater than the maximum expiratory effort of which the animal is capable, provided the pressure is maintained, air will leave the alveoli and enter the pulmonary capillaries. Enough air may thus be forced into the circulation to cause death, and the effect is, of course, the same as though the air had directly entered a pulmonary vein. Ewald and Kobert,[13] in a painstaking study,

6. Schlaepfer, K.: Bull. Johns Hopkins Hosp. **33**:321, 1922. Wever, E.: Beitr. z. Klin. d. Tuberk. **31**:159, 1914.

7. Walcher, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:314, 1926. Steindl, H.: Wien. klin. Wchnschr. **37**:206, 1924.

8. Herxheimer, quoted from Infeld, M.: Wien. klin. Wchnschr. **27**:1407, 1914.

9. Otto, W., quoted from Geipel: München. med. Wchnschr. **59**:1683, 1912.

10. Lubarsch and Ostertag, quoted from Steindl, H.: Wien. klin. Wchnschr. **37**:206, 1924.

11. Kaufmann, quoted from Steindl, H.: Wien. klin. Wchnschr. **37**:206, 1924.

12. Bichat, quoted from Beneke, R.: Verhandl. d. deutsch. path. Gesellsch. **16**:263, 1913.

13. Ewald, J., and Kobert, R.: Arch. f. d. ges. Physiol. **31**:160, 1883.

"Ist die Lunge luftdicht?," showed that this phenomenon is not one of alveolar rupture but of escape of air through normal stomas in the alveolar walls when a certain degree of distention is reached. On this principle has been explained the finding of air occasionally in the cavity of the left side of the heart of persons drowned [14] or hanged [15] and of infants who have received strenuous resuscitative measures.[16] Neubürger [17] suggested that the convulsions which sometimes occur in whooping cough are from cerebral embolism, air being forced into the blood stream from the alveoli during a paroxysm of coughing. At autopsy in these cases confirmatory evidence is found in the lesions of the brain.[18]

CLINICAL CASES

CASE 1.—A man, aged 42, had an illness of sixteen months' duration. The onset was insidious, with cough, fever, night sweats and progressive loss of weight. The sputum was abundant and fetid, and was constantly negative for tubercle bacilli. The diagnosis was bronchiectasis of the left lung and chronic empyema.

He was admitted to University of Iowa Hospital surgical service. A small empyema pocket in the left side of the chest was drained by rib resection. Some time later, by roentgen examination, a cavity was found in the left lung, and surgical drainage of the cavity was undertaken. With the patient under ethylene anesthesia, a piece of rib was removed at the posterior axillary line over the cavity. The pleural surfaces were found adherent, and an exploring needle, attached to a syringe, was passed into the lung. The resistance offered to the needle by the parenchyma of the lung was increased. At some points air was aspirated freely, at others blood. No pus was found and after a few punctures the attempt was abandoned. As the wound was being closed, the patient suddenly ceased to breathe and heart action could not be detected.

At autopsy, about one hour after death, air was found in large quantities in the blood vascular system. The right side of the heart and pulmonary artery were distended with bloody froth. The left side of the heart was empty. Air was present in the aorta and its main branches, and beads of air were plainly visible in the coronary arteries, the mesenteric arterioles and such small arteries as were exposed by dissection. The veins everywhere were free from air, except for the portal vein and the great veins near the right side of the heart, which contained large amounts. The left lung was fibrous, contracted and adherent to the wall of the chest throughout, except where there was a small empyema cavity. This cavity communicated with the surface through an old thoracotomy wound. After the left lung was removed, the integrity of its bronchial tree was tested by filling it with water. The water returned immediately by way of the pulmonary vein of the upper lobe. In the left primary bronchus was found a papillary carcinoma nearly obstructing the lumen. On section, the lung proved to be fibrotic throughout and was riddled with saccular bronchiectatic cavities. Dissection failed to show a precise point of communication between the bronchial tree and the pul-

14. Paltauf, quoted from Walcher, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:314, 1926.

15. Iversen, A.: Vrtljschr. f. gerichtl. Med. **22**:226, 1862.

16. Lindblom, A.: Virchows Arch. f. path. Anat. **252**:197, 1924.

17. Neubürger, K.: Klin. Wchnschr. **4**:113, 1925.

18. Husler, J., and Spatz, H.: Ztschr. f. Kinderh. **38**:428, 1924.

monary vein, although a clot of fresh blood was found in a bronchiectatic cavity in the upper lobe at a point roughly corresponding to the site of thoracentesis. The right lung was normal, and observations elsewhere were unimportant.

The diagnosis was: carcinoma of the left primary bronchus, bronchiectasis, chronic empyema, bronchovenous fistula and air embolism from the pulmonary vein.

EXPERIMENTAL WORK

Proof by experiment was sought for the theorem suggested by this case: Given a bronchovenous communication, the pressure relationships within the bronchi and veins in a closed chest during life are such as to transfer air from bronchus to vein. Four dogs were used. A bronchovenous fistula was produced within the intact chest in such a manner that communication could be established or abolished at will and the passage of substances through the fistula could be observed.

Dog 1, weighing 10 Kg., was given positive pressure ether anesthesia. The chest was opened through an intercostal incision on the right and the hilum of the lung was exposed. A glass cannula filled with sodium citrate solution was tied into the pulmonary vein of the lower lobe. Another cannula was fixed in the wall of the accompanying bronchus, and the two cannulas were led out of the chest and connected with a short piece of rubber tubing, temporarily clamped off. The lungs were then inflated to exclude pneumothorax and the chest wound closed tightly about the cannulas. The dog was then allowed to recover consciousness fully.

While the animal was walking about, the clamp was suddenly removed from the connecting tube and communication was established between the bronchus and vein. With the next inspiration, the solution in the cannula passed quickly into the vein and was followed by air, as evidenced by the behavior of a little solution that remained in the bend of the tube. The next two or three inspirations each drew more air into the vein, and then the flow was reversed filling the tube with blood. Almost immediately after the first inspiration the dog appeared uncomfortable, and the hind quarters began to drag; paralysis spread and in a few seconds the dog fell to the floor unconscious. There followed focal and general convulsions, labored breathing, extreme rotation of the eyeballs and wide dilatation of the pupils. At about three minutes, muscular relaxation occurred, respirations became feeble and soon ceased. Heart action continued for a minute or so.

Autopsy revealed that the relations within the chest were normal except for the artificial connection between the bronchus and vein. Quantities of air were contained in the vascular system.

DEDUCTIONS

A bronchovenous fistula may be created in man by the passage of an exploring needle into firmly indurated lung tissue. Given such a communication, the relation of bronchial to venous pressures during inspiration is such as to pass air from bronchus to vein and to give rise to fatal air embolism.

DISTRIBUTION OF AIR IN THE CIRCULATION

Gundermann [19] opened the chest of dogs widely with the animals under positive pressure anesthesia and injected air directly into a

19. Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:261, 1921.

pulmonary vein. It appeared to him that the air was distributed by the heart evenly and in proportion to the size among the peripheral arteries, until just before death, when because of a weak heart action the branches of the aorta lying near the heart received a larger share. He observed air bubbles immediately entering the coronary arteries and riding there without a tendency to pass on through the capillaries, and he concluded that air cannot pass any capillary bed. Heller, Mager and von Schrötter,[20] on the other hand, observed air bubbles travel through the mesenteric circulation, and Beneke [21] found air accumulated in large quantities in the right side of the heart, when injection had been made into the peripheral arteries.

That position of the body affects in some degree the distribution of the air in this form of air embolism was suspected by Schlaepfer,[22] for he noticed that bubbles could be seen in the retinal vessels of dogs only when the head was held up.

EXPERIMENTAL WORK

The distribution of air received into the pulmonary veins in the vascular tree was studied in dogs under varied circumstances of dosage and body position. The manner of inducing embolism was uniform: With the animals under positive pressure anesthesia, the chest was opened and a glass cannula, filled with sodium citrate solution and temporarily obstructed at the outer end, was fastened in the branch of the pulmonary vein from the lower lobe of the lung and led out of the chest. The chest was closed, residual pneumothorax being avoided. The anesthetic was then discontinued and air was injected through the cannula with a syringe at a uniform rate of 25 cc. per minute. At death, or when the animal was killed, a systematic examination was made of the vascular system.

The experiments may be grouped in accordance with the position of the animal. Representative protocols are as follows:

Group 1: Position Horizontal, Sixty-Seven Dogs.—EXPERIMENT 1.—Dog 21, weighing 16 Kg., was placed on the left side in the horizontal position, and an amount of air equal to 3.9 cc. per kilogram of body weight was injected into the pulmonary vein. Death occurred in nine minutes.

At autopsy, the right side of the heart and adjacent great veins were found moderately distended with air. The pulmonary arteries were filled with air; the left side of the heart and pulmonary veins were free. There were a few air bubbles in the coronary arteries and veins. The aortic arch was partly filled with air, but the descending aorta throughout contained none. The carotid, axillary, internal mammary, intercostal and femoral arteries on the right side

20. Heller, R.: Mager, W., and von Schrötter, H.: Ztschr. f. klin. Med. **32:** (suppl.) 113, 1897.

21. Beneke, R.: Verhandl. d. deutsch. path. Gesellsch. **16:**263, 1913.

22. Schleapfer (footnote 6, first reference).

held considerable amounts of air, while the corresponding vessels on the left were relatively free. The mesenteric arteries were beaded with bubbles. Air was found only in the femoral, portal, internal mammary and jugular veins.

In other dogs of this survival time the distribution of air was essentially the same. Those dying more rapidly (in from one to two minutes) showed air still in the left side of the heart and confined largely to the arteries. Little was found in the large veins or right side of the heart. Animals living longer than dog 21 (from twenty to thirty minutes) had little or no air in the right side of the heart and veins and reduced amounts in the peripheral arteries. The coronary arteries were regularly free. A constant and striking observation was unequal distribution, for vessels lying uppermost in the body, here in the right side, were always much more abundantly supplied with air. This evidence of air buoyancy

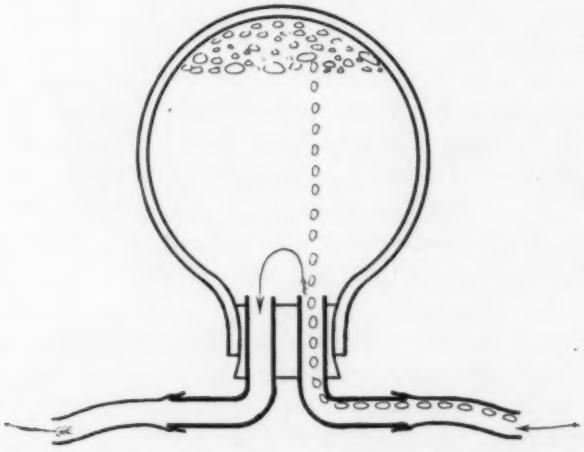

Fig. 1.—Air trap used to study the distribution of air.

was displayed also in the aortic arch. The first portion of the arch lay uppermost and accumulated air from the blood passing through. This air drained off largely into the great vessels of the neck, and the result was to distribute a greater portion of the air to the head, neck and upper extremities than would be indicated from the size of the vessels.

In a few of these dogs, the distribution of air was studied more exactly by interposition of air traps in the blood stream at various points. The air trap (fig. 1) was a small inverted flask with afferent and efferent cannulas. The circulating blood was rendered incoagulable by the intravenus injection of 20 mg. of heparin per kilogram of body weight. The vessel in question was then exposed and divided and the two ends connected with the trap cannulas, the trap being first filled with blood. When adjusted, the trap thus became a part of the vascular system, and by retaining air which passed through the vessel permitted estimation of its appearance time and amount.

EXPERIMENT 2.—Dog 65, weighing 13 Kg., was fitted with traps in both carotid arteries. Three and nine-tenths cubic centimeters of air per kilogram of body weight (50.7 cc.), which is a lethal dose, was injected into the pulmonary vein in the routine manner. Almost instantly after the injection was started air bubbles began to appear in the traps and continued to do so only as long as the injection lasted. The dog recovered; it was killed at one hour.

At autopsy, air was found distributed in the vessels as usual, except that the carotid arteries were free. Twenty-seven cubic centimeters of air was recovered from the traps, i. e., more than half that injected.

EXPERIMENT 3.—Dog 38, weighing 12 Kg., was fitted with traps in both vena cavae, and 3.9 cc. of air per kilogram of body weight (46.8 cc.) was injected into the pulmonary vein. At one minute and twenty seconds, bubbles of air began to appear in the trap of the superior vena cava. No air entered the other trap. Death occurred in ten minutes.

Autopsy showed air to be distributed in the usual manner, except that the right side of the heart and pulmonary arteries were free. Three cubic centimeters of air was present in the trap of the superior vena cava. This amount could obviously not be taken to represent the quantity ordinarily returning to the heart after this dosage of air, since the presence of the traps in the cavae impeded the driving force of the heart to a considerable degree.

Group 2: Position Vertical, Head Down, Sixty-Six Dogs.—Dog 109, weighing 17 Kg., was raised to a vertical position, head down, and 3.9 cc. of air per kilogram of body weight was injected into the pulmonary vein. Death occurred at seventeen minutes.

Autopsy revealed that air filled the coronary arteries and the arteries and veins of the trunk and hind legs. None was found in the vessels of the head, neck and forelegs, nor in the vena cavae, right side of the heart or pulmonary arteries.

In all of these animals, the pattern of distribution was constant. The vessels caudad to the heart alone received air. The coronary arteries contained much more air than with the dog in the horizontal position, and often the blood was entirely replaced by air, giving the vessels the appearance of silver threads. Occasionally, the left ventricle, being inverted, retained a considerable quantity of air indefinitely. No air returned to the right side of the heart.

The observations were corroborated in part by experiments using traps in various vessels.

Group 3: Position Vertical, Head Up, Nineteen Dogs.—Dog 47, weighing 5.5 Kg., was placed in a vertical position, head up, and 3.9 cc. of air per kilogram of body weight was injected into the pulmonary vein. Death occurred in five minutes.

Autopsy revealed that air filled the vessels of the head, neck and forelegs. A small amount was found in the right side of the heart and pulmonary arteries and a few bubbles of air only were contained in the coronary arteries.

In this group of animals again a constant pattern of air distribution was presented, which was complementary in type to that for the group with the head down. Only the vessels taking origin from the aorta cephalad to the heart received air. The coronary arteries were involved to a minimal degree.

DEDUCTIONS

Air that enters the circulation by way of the pulmonary vein follows the course of the blood stream in general but with uneven distribution. Instead of being divided among the vessels in amounts according to their sizes, the air tends to float on the blood and to seek the upper parts of the body. Even where the stream is rapid and violently churned, as in the heart and aorta, air and blood fail to mix thoroughly; the air may remain stationary in a bend of the vessel, or, should gravity so dictate, it may even pass in the direction opposite to that of the blood.

This influence of air buoyancy on the distribution determines distinct differences in various positions of the animal. A typical pattern of embolism with but slight individual variation is found in any given position. Thus, in the dorsal recumbent, horizontal position, air quickly leaves the pulmonary vein and left side of the heart and passes into the aorta. The arch of the aorta is distinctly higher than the descending portion of that vessel and acts as a trap to hold a large part of the air and pass it into the great arch branches. Thus, more than half of the air may go to the head, neck and upper extremities. Distributed in this uneven manner, the air in the form of bubbles is driven to the periphery. The capillaries hinder but do not prevent passage, and after a minute or so air begins to return by the veins of the parts affected to the right side of the heart, whence it is thrown into the lesser circulation. No air succeeds in traversing the pulmonary capillaries but it is held in the pulmonary arterial tree, obstructing the lesser circulation partially and gradually disappearing by excretion into the alveoli and by absorption into the blood and tissues. Air remains longest in the peripheral arteries, sometimes for several hours, for a shorter period in the pulmonary arteries, right side of the heart and great veins, no longer than one-half hour in the coronary arteries and for only a few seconds in the pulmonary veins and left side of the heart. Thus, the period of time that elapses between embolism and death determines largely the position of the air at autopsy.

With the animal in a vertical position, air is distributed only to those parts lying above the level of the heart. Accordingly, when the head is up, the head, neck and forelegs receive the air totally, except for a slight amount in the coronaries; when the head is down, the trunk and hind legs receive the air, and the coronaries are heavily involved.

PHYSIOLOGIC REACTION, TOLERANCE AND CAUSE OF DEATH

The symptoms in man in air embolism from the pulmonary vein are separable more or less distinctly into two types, neuromuscular and cardiovascular. In a given case, both types may be equally represented, or one may predominate even to the exclusion of the other.

The nervous symptoms are extremely various and occur in different combinations in each instance. The onset may be precipitous with immediate unconsciousness and death, or it may be ushered in more gradually, beginning with dizziness, faintness, local or general paresthesias, aphasia and visual disturbances. More serious symptoms are paraplegia and hemiplegia, blindness, focal and general convulsions, unconsciousness, hyperpnea, Cheyne-Stokes respiration and unequal, dilated and reactionless pupils. Death may occur at any time, and has been known to be delayed as long as six days. When delayed, an unconscious state predominates with periodic convulsions. At any stage, the symptoms may begin gradually to disappear and the patient to recover. Persistent paralyses have occurred.

Cardiovascular symptoms consist in pulse irregularities, asphyxial signs and evidences of gradual or sudden heart failure. Patches of marble-like discoloration are sometimes found on the skin. These symptoms are seen alone when the patient is under general anesthesia and nervous reactions are inhibited, or when the amount of air is overwhelming and nervous effects do not have time to develop. Detailed discussion and illustration of symptoms are given by Schlaepfer.[22]

The degree of tolerance in man for air entering the circulation from the pulmonary vein is not known, although it is understood to be much less than that from a peripheral vein. In certain instances, as in the case reported by von Adelung,[23] the amount of gas injected for pneumothorax at the time of air embolism was known, but what part of that actually entered the circulation could not be determined. In animals, Gundermann [19] alone has estimated tolerance. Using dogs, he opened the chest with the animals under positive pressure anesthesia and injected air into a pulmonary vein, and found that even 1 cc. slowly introduced was immediately fatal. The unnatural circumstances of the experiments, however, probably rendered the animals abnormally susceptible.

It is generally appreciated that the tolerance of a person for air embolism depends largely on the rate of entrance of air into the circulation.

In air embolism from the peripheral vein the tolerance has been studied experimentally by several investigators. Ilyin [24] noted that dogs withstand as much as 2,000 cc. of air injected into the jugular vein at a rate of 30 cc. per minute with 10 mm. of mercury pressure. The dose per kilogram of body weight was not estimated. In twenty-five rabbits, Jehn and Nägeli [25] found the maximum tolerance to be 0.89 cc.

23. Von Adelung, E.: A Case of Gas Embolism, J. A. M. A. **69**:1522 (Nov. 3) 1917.

24. Ilyin, F.: J. Akush. i Jhensk. Bolïez. **28**:72, 1913.

25. Jehn, W., and Nägeli, T.: Ztschr. f. d. ges. exper. Med. **6**:64, 1918.

per kilogram of body weight; in six cats, 2.5 cc. per kilogram; and of two dogs, one survived 5.3 cc. and one died from 7.7 cc. per kilogram. The rate of the injection was not given. Richter [26] stated that in dogs 20 cc. of air produced alarming symptoms and 250 cc. was lethal; in horses, the corresponding amounts were 1,000 and 8,000 cc. No body weights, injection rates or numbers of animals were given. Many other investigators have contributed less accurate data. It is to be concluded that different species present widely different tolerances and among individuals of a single kind there is variation. The values in man are again not known.

The cause of death in air embolism from the pulmonary vein was referred by Gundermann [19] to heart failure, after observing in his dogs immediate myocardial incapacity following the entrance of air into the coronary arteries. He pointed out that heart action ceased too soon to allow involvement of the brain to play a part. Beneke,[27] at autopsy in man, found much air in the right side of the heart and pulmonary arteries and suggested that death was due to obstruction of the lesser circulation, as in air embolism arising from a peripheral vein. The fallacy of this assumption was indicated by Gundermann in the fact that an amount of air which is lethal when entering the pulmonary vein is readily tolerated when injected into a peripheral vein. The majority of authors agree with Brauer [28] and his school in ascribing death to brain embolism, since nervous symptoms frequently predominate and at death respirations usually cease long before heart action. Wever [29] injected air into the carotid artery of dogs and monkeys and produced a symptom complex similar to that of man. The brains of Wever's animals were examined by Spielmeyer.[30] Those that survived more than fifteen hours presented focal ischemic necrosis distributed irregularly, chiefly in the cerebral cortex, and characterized by degenerative alterations in the ganglion cells and glial proliferation. The degree was in proportion to the amount of air and to the period of time between embolism and death. The same changes were found in cases in man. Gold [31] described the brain of a person who died six days after cerebral air embolism, and in addition to the alterations mentioned, indicated edema of the whole brain and petechial hemorrhages in the medulla oblongata and pons.

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26. Richter, quoted from Hutter, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **40**:131, 1927.

27. Beneke, R.: Beitr. z. Klin. d. Tuberk. **9**:343, 1908.

28. Brauer (footnote 2, second reference).

29. Wever (footnote 6, second reference).

30. Spielmeyer, W.: Verhandl. d. Kong. f. inn. Med. **30**:359, 1913.

31. Gold, E.: Arb. a. d. neurol. Inst. a. d. Wien. Univ., 1924, vol. 26.

CLINICAL CASES

Case 1, already described, illustrates the purely cardiovascular type of symptomatology, and case 2, to be described, the neuromuscular type.

EXPERIMENTAL WORK

Physiologic Reaction.—The reaction of the dog to air injected into the pulmonary vein was studied under varied experimental circumstances. The doses, determined according to the body weight, ranged from amounts easily borne to those immediately fatal. Three positions were employed, as in the preceding experiments. The method was the same in all instances:

A cannula was placed in a pulmonary vein. The femoral artery was cannulated and connected with a mercury manometer. With the

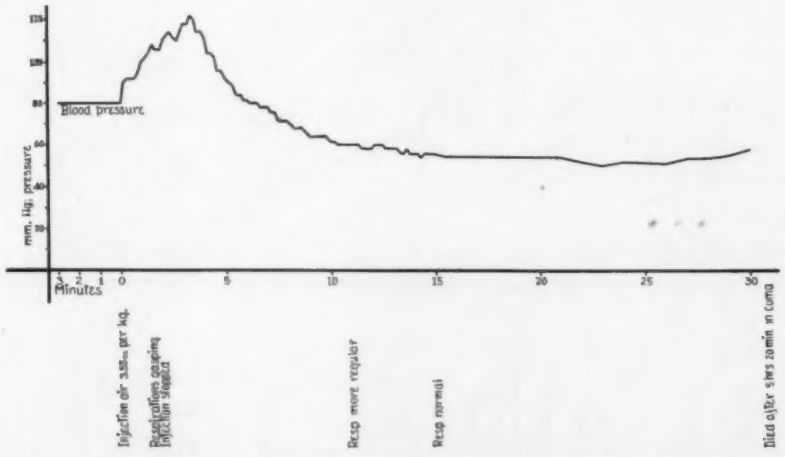

FIG. 2 (dog 20).—Injection of air into the pulmonary vein, with the dog in the horizontal position. Moderately severe reaction.

animal under ether anesthesia, respiration and blood pressure were observed, and when they had been constant for three minutes, the ether mask was removed and the dose of air injected into the cannula of the vein at a rate of 25 cc. per minute. The reaction was noted in detail.

Typical protocols are as follows:

Group *a*: Position Horizontal, Sixty Dogs: EXPERIMENT 1.—Dog 20, weighing 16 Kg., received 3.55 cc. of air per kilogram of body weight and displayed a moderately severe reaction (fig. 2).

At one minute thirty seconds, respiration became gasping and irregular; at eleven minutes, more regular, and at fifteen minutes, normal.

At two minutes, the injection of air was complete.

At three minutes twenty seconds, the blood pressure, which had begun to rise with the beginning of the injection of air, reached a maximum of 40 mm. of

mercury above normal. It then fell gradually to a minimum of 30 mm. of mercury below normal at twenty-three minutes. It was commencing to rise when the readings were stopped.

The pulse was regular and strong throughout.

Unconsciousness continued, although no more anesthesia was administered. After one hour twitching contractions of the legs and walking movements began. The muscles were spastic and at times the decerebrate posture of Sherrington was assumed. The dog moaned and howled now and then, although obviously unconscious. No cardiorespiratory irregularities were noted. After four hours, consciousness returned sufficiently to permit vague recognition of surroundings and unsteady walking, but this was temporary and death occurred in deep unconsciousness at five hours twenty minutes.

EXPERIMENT 2.—Dog 28, weighing 22 Kg., received 3.9 cc. of air per kilogram of body weight and presented a severe reaction (fig. 3).

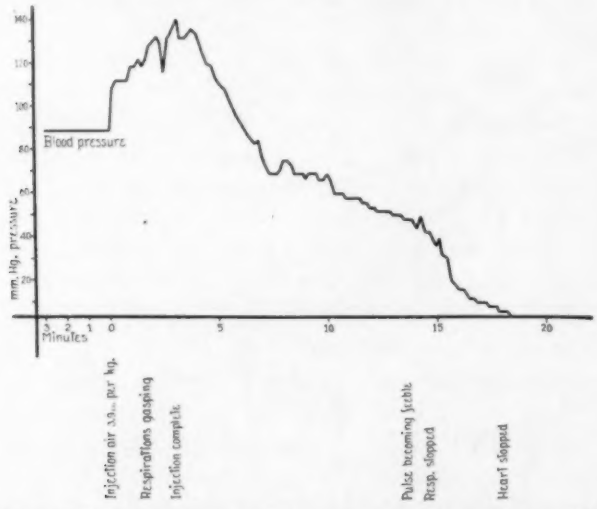

FIG. 3 (dog 28).—Injection of air into the pulmonary vein, with the dog in the horizontal position. Severe reaction.

At two minutes, respirations were gasping. There were periods without breathing. At fifteen minutes, breathing ceased.

At three minutes twenty seconds, the injection of air was complete.

At three minutes ten seconds, the blood pressure, which began to rise with the injection of air, reached a peak of 52 mm. of mercury above normal, and then fell jerkily to 0 at eighteen minutes twenty seconds.

The pulse remained regular and full until the fourteenth minute, when it became increasingly feeble; it ceased at eighteen minutes twenty seconds.

Others of these dogs, receiving smaller doses, showed reactions during the first half hour similar to those of dog 28, but less severe and usually followed by recovery. There was always a period of unconsciousness beyond that to be expected from the anesthetic.

Group *b*: Position Vertical, Head Down, Thirty-Two Dogs: EXPERIMENT 1. —Dog 70, weighing 23.6 Kg., received 1.22 cc. of air per kilogram of body weight and presented a moderately severe reaction (fig. 4).

Respirations were affected at no time.

At one minute, the injection of air was complete.

At ten seconds, the blood pressure rose 20 mm. of mercury, dropped almost immediately and remained about 10 mm. of mercury below normal.

At fourteen minutes, the pulse, thus far regular and strong, suddenly began to skip beats, often two or three together, and blood pressure took wide drops. This irregularity continued twenty minutes and suddenly stopped. The pulse continued normal.

At five minutes, consciousness began to return and ether had to be readministered. At thirty minutes, ether was discontinued and the apparatus disconnected. The dog began to awaken as ordinarily from anesthesia and showed no effects of embolism.

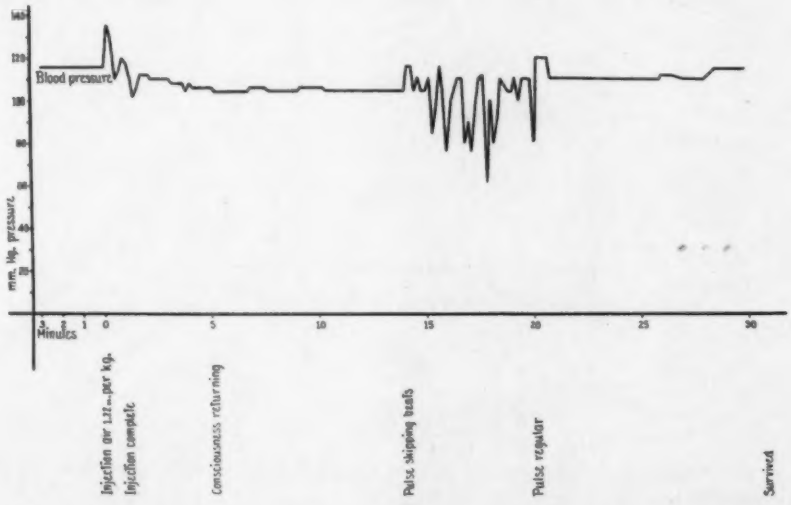

FIG. 4 (dog 70).—Injection of air into the pulmonary vein, with the dog in the head-down position. Moderately severe reaction.

EXPERIMENT 2.—Dog 66, weighing 18.1 Kg., received 1.22 cc. of air per kilogram of body weight and had a severe reaction (fig. 5).

Respirations were normal until the fourteenth minute, when they abruptly failed and represented the last sign of life.

At one minute, the injection of air was complete.

At twenty seconds, the blood pressure was 20 mm. of mercury above normal. It dropped slightly and then rose to a level of from 10 to 15 mm. of mercury above normal. At thirteen minutes, the heart action, which had till then been strong and full, suddenly failed and the blood pressure dropped precipitously to 0 at fourteen minutes.

Dogs in this position showed only cardiovascular symptoms. Heart block was frequent and characteristic and was the cause of death, rather than the gradual myocardial failure seen in the horizontal position.

With large doses, sudden, total block occurred very early; with smaller amounts, total block appeared as abruptly but after from ten to twenty minutes of fairly normal course immediately preceded or not by a few dropped pulse beats, or a period of dropped beats (partial block) came and went without warning, followed by recovery. No heart block was initiated after thirty minutes. In none of the animals were there signs of involvement of the central nervous system. There was no interference with consciousness.

Group *c*: Position Vertical, Head Up, Eighteen Dogs: Dog 48, weighing 9.1 Kg., received 3.9 cc. of air per kilogram of body weight and presented a severe reaction (fig. 6).

At thirty seconds, the respirations were shallow and gasping; they ceased at one minute.

At one minute ten seconds, the injection of air was complete.

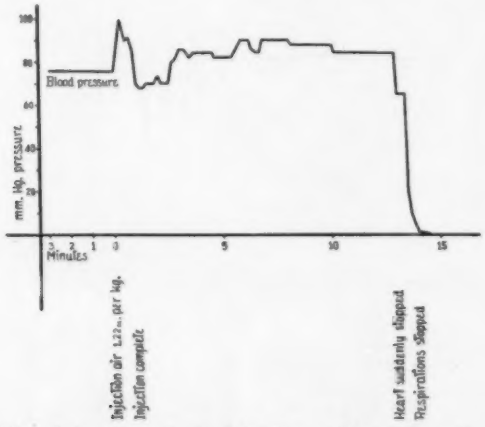

FIG. 5 (dog 66).—Injection of air into the pulmonary vein, with the dog in the head-down position. Severe reaction.

At twenty seconds, the blood pressure had risen to 38 mm. of mercury; it dropped immediately to 0 at four minutes.

At two minutes, the pulse became weak, and the heart action ceased at four minutes as the last sign of life.

Other dogs that received smaller doses exhibited less severe reactions, but none recovered. The respirations were almost instantly affected and permanent cerebral injury with unconsciousness occurred with the smallest doses. The heart showed no disturbance until some time after respirations ceased.

Group d: Investigation of Blood Pressure Reaction, Ten Dogs: The cause of the initial elevation in blood pressure that appears characteristically in air embolism from the pulmonary vein was investigated. Possible causes for this are direct cardiac effects, action on the central nervous system and action directly on the blood vessels. The last

appeared the most likely, for air accumulates in the peripheral arterioles and capillaries and probably increases resistance to blood flow. The first two possibilities were eliminated by experiment, as follows:

With the animals under ether anesthesia, a cannula was inserted in an intercostal artery, pointing toward the aorta. With the dog horizontal, air was injected through the cannula and intercostal vessel into the descending aorta at a rate of 25 cc. per minute. Various doses of air were employed.

Dog 40, weighing 22.4 Kg., received 3.9 cc. of air per kilogram of body weight (fig. 7).

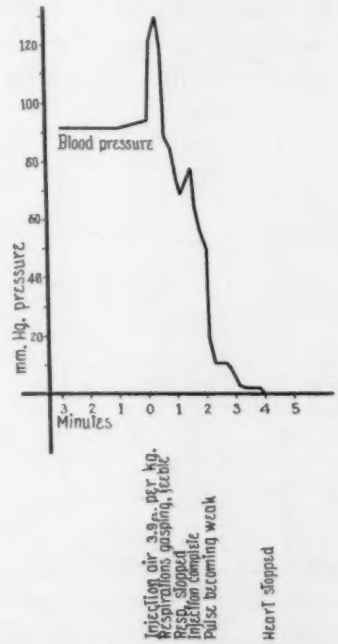

FIG. 6 (dog 48).—Injection of air into the pulmonary vein, with the dog in the head-up position. Severe reaction.

The respirations and pulse were affected at no time.

The blood pressure commenced to rise immediately after the injection was started and reached 40 mm. of mercury above normal at thirty seconds. This elevation was maintained for five minutes, when the pressure returned to normal.

At three minutes thirty seconds, the injection of air was complete.

Autopsy showed no air to have entered the coronary arteries or vessels of the head, neck and forelegs.

Tolerance.—The tolerances for air injected into the circulation at various points were compared:

With the animals under ether anesthesia, the pulmonary vein was cannulated in twenty-one dogs, the jugular vein in twenty-six dogs and

the seventh intercostal artery (descending aorta) in ten. Into each dog was injected an amount of air determined according to the body weight and varied from dog to dog, with the purpose of finding the maximum tolerance dose. The rate of injection was 25 cc. per minute. After four hours the outcome was noted, whether by death or by recovery.

The results are charted in figure 8. Here each of three columns represents the greatest amount of air per kilogram of body weight withstood in one of the forms of air embolism. The figures inserted in each column specify the numbers of dogs used, and the positions of the figures indicate the doses and the fates of the dogs. Thus, the maximum tolerance dose for the pulmonary vein is 1.5 cc. per kilogram, while those for the jugular vein and descending aorta are 76 and 70

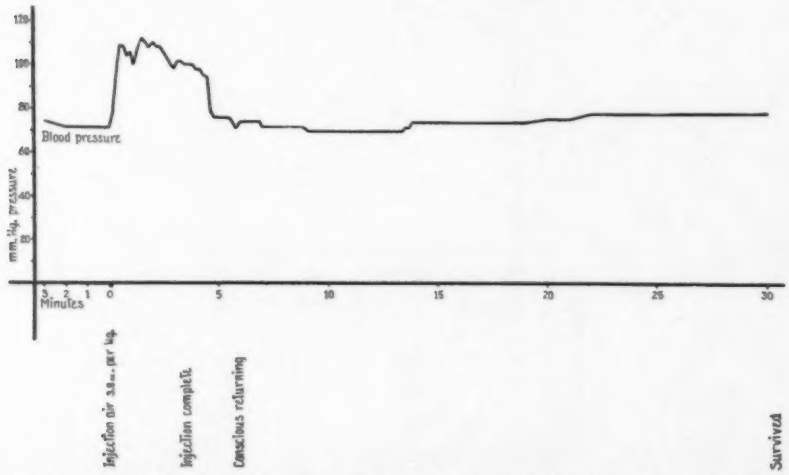

FIG. 7 (dog 40).—Injection of air into the intercostal artery (aorta), with the dog in the horizontal position.

cc., or at least fifty times as great. Considerable individual variation is evident.

The tolerance for air injected into the pulmonary vein was determined for various positions of the body, with twenty-one dogs in the horizontal position, seventeen with the head up and thirty-two with the head down.

The results are charted in figure 9, the same method being employed as for the preceding chart. The maximum tolerance dose is 0.5 cc. per kilogram of body weight with the head up, 1.5 cc. or three times as great in the horizontal position, and 3.3 cc. or six and one half times as great with the head down. Individual variation presents itself.

Cause of Death.—The observations recorded concerning the symptomatology and distribution of the air suggest that the cause of death differed in certain body positions. With the head up, the air ascended

and involved the brain massively. Death resulted either early from respiratory failure (embolism of the medulla oblongata) or, later from decerebration.

In the head-down posture, the air ascended caudally. The coronary arteries were affected most seriously. The heart instantly ceased to beat or, with smaller doses, it continued for a few minutes and then underwent heart block. The brain was protected from embolism and played no part in the cause of death.

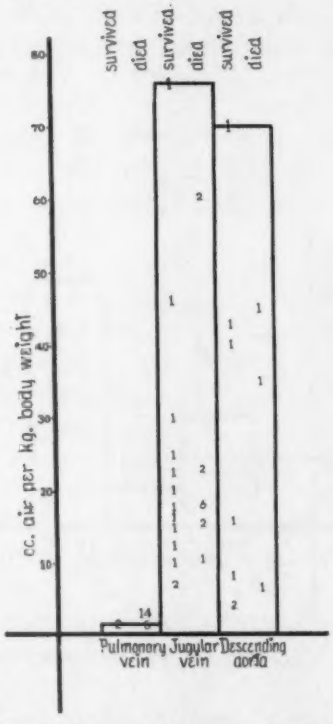

FIG 8.—Tolerance for air injected into the circulation at various points.

In the horizontal position, the air passed to both brain and coronary vessels. In certain instances, the symptoms preceding death suggested involvement of the brain as the lethal factor; in others, coronary involvement. To test the relative importance of these two factors in this position, experiments were devised wherein the brain was protected from air embolism:

With the animals under ether anesthesia, air traps were placed in both carotid arteries. Both vertebral arteries were ligated. A strand of wire was twisted tightly about the neck, including all structures except the carotid arteries, jugular veins, vagus nerves and trachea. Thus, the only blood supply remaining to the brain was through the

trapped carotid vessels. Three and nine-tenths cubic centimeters of air per kilogram of body weight, which is a lethal dose, was then injected into a pulmonary vein. Seven dogs were used.

Dog 32, weighing 11.5 Kg., did not present symptoms referable to embolism. The animal recovered. At one hour, the dog was killed.

Autopsy revealed that the distribution of air was typical of that of pulmonary vein air embolism in this position, except that the head and neck were free. The traps contained 32 cc. of air.

In one other dog, the result was the same. In five dogs, death occurred within a few minutes after embolism.

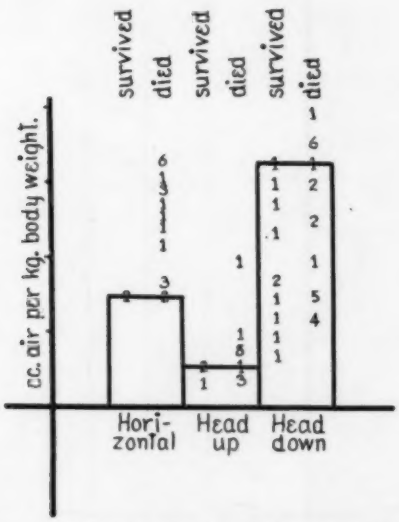

FIG. 9.—Tolerance for air injected into the pulmonary vein in various positions.

DEDUCTIONS

These animals were under general anesthesia at the time of the injection of air, and during the first ten to twenty minutes the symptomatic effects of embolism of the higher brain centers were necessarily eliminated. This part of the picture is supplied, however, in the experiments in the section on etiology.

The symptomatology was found to be similar in all details to that in man, and to be separable into two types, i.e., neuromuscular and cardiovascular. Extreme variation in appearance and degree also occurred, even with the same amounts of embolus.

There were two well defined periods in the reaction, acute and chronic. The acute period lasted up to one-half hour and was characterized by disorders of respiration, heart function and blood pressure, together with irritative and paralytic effects in the higher brain centers.

The chronic period presented states of semidecerebration or total decerebration, delirium, semilucid periods and convulsive seizures. Improvement leading to recovery was seen at any stage but was rare after three hours. The severity of symptoms was in proportion roughly to the amount of embolus; death occurred in either period.

The type of symptoms was determined largely by the position of the animal. In the vertical position, head up, the neuromuscular type was dominant, and the only cardiovascular effect detectable was the elevation of the initial blood pressure. In the vertical position, head down, cardiovascular responses alone appeared. With the dog horizontal, both types occurred and in varying proportions but the neuromuscular usually predominated.

A constant symptom was the elevation of the initial blood pressure. Evidence was obtained that this resulted from the accumulation of air bubbles in the peripheral arterioles and capillaries with increased resistance to arterial blood flow.

The tolerance of the dog for air injected into the circulation depends largely on the portal of entry. In the jugular vein or descending aorta more than fifty times as much may be withstood as in the pulmonary vein. In the pulmonary vein tolerance depends on body position, and is least in the head-up position, three times as great in the horizontal and six and one-half times as great in the head-down position.

The fatal effects of air embolism from the pulmonary vein are due to impairment of three vital functions; i. e., cardiac activity by the obstruction of the coronary arteries, cerebral and medullary function by blockage of the arteries of the brain and blood circulation by blockage of the pulmonary arteries. Either the first or the second may be the primary cause of death; the third is never more than contributory. The first is the sole cause of death when the animal is in the head-down posture and the mechanism is by heart block; the second alone causes death when the animal is situated head up, with respiratory paralysis in the early stage or decerebration later; in the horizontal position all three contribute and the first or the second may be primary, depending on the chance distribution of the air embolus.

DIAGNOSIS AND PROGNOSIS

The diagnosis of air embolism from the pulmonary vein has been made without difficulty when sucking was heard at an open vessel or when gas was injected into the chest immediately before the symptoms. Becker,[32] Stargardt,[33] Perthes [34] and others have been led by the visual

32. Becker, E., quoted from Brauer, L.; Schröder, G., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, J. A. Barth, 1923, vol. 2, p. 461.

33. Stargardt, quoted from Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:261, 1921.

34. Perthes, quoted from Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:261, 1921.

disturbances in some of these cases to examine the eyegrounds and were able to establish a diagnosis by seeing bubbles in the retinal vessels. A large proportion of the cases, however, have probably remained obscure from lack of direct evidence. Often the portal of entry of air or gas into the circulation was not apparent, nor was there a sucking sound; no heart murmur occurred to point to the diagnosis, as in air embolism from a peripheral vein; an ophthalmoscope has rarely been at hand.

The symptomatology has not assisted greatly in diagnosis, due to confusion with that of other forms of sudden collapse, i.e., internal hemorrhage, surgical shock, heart failure, the syncope that ensues with the rapid removal of much fluid from the pleural cavity and pleural reflex. The last of these, otherwise known as pleural eclampsia or pleural shock, has contributed chiefly to the confusion, for it is believed by many that nerve impulses elicited from the pleura and lung by trauma from an instrument are capable of producing all symptoms seen in air embolism. The nature of such nerve reflexes has been studied. Brodie and Russell [35] demonstrated strong vagal responses in animals obtained by stimulation of vagal fibers at the hilum, bronchi and alveoli of the lung. Sauerbruch [36] saw sudden heart failure in man immediately following mass ligation at the hilum of the lung or probing within a bronchial fistula. Johnson and Luckhardt [37] found that sudden, forceful inflation of the lungs in man and animals results in vagus reflex that profoundly slows the heart and depresses the blood pressure, often fatally, and Johnson and Van Allen [38] proved that this reflex originates from the vagus fibers in the lung. Moreover, the experimental work of Capps and Lewis [39] indicated the presence of two powerful reflexes, one vagal and resulting in cardiac inhibition and the other vasomotor with dilator influence on the peripheral vessels. These could be obtained separately or at once by irritation of the inflamed but not of the normal pleura. The cardio-inhibitory reflex was in itself insufficient to cause death but the vasomotor effects were frequently not recovered from; both served to lower the blood pressure profoundly. Thus, it is proved that what may be termed pleural reflex exists in both man and animals and that inhibition of the heart rate, peripheral vasodilatation and fall in the blood pressure occur and may result in death. On the other

35. Brodie, T., and Russell, A.: J. Physiol. **26**:92, 1900.

36. Sauerbruch, F.: Chirurgie der Brustorgane, Berlin, Julius Springer, 1925, vol. 2, p. 160.

37. Johnson, C. A., and Luckhardt, A. B.: Am. J. Physiol **83**:642, 1928; ibid. **84**:453, 1928.

38. Johnson, C. A., and Van Allen, C. M.: Unpublished work.

39. Capps, J. A., and Lewis, D. D.: Am. J. M. Sc. **134**:868, 1907; Blood-Pressure-Lowering Reflexes from Irrigation of the Chest in Empyema, Arch. Int. Med. **2**:166 (Sept.) 1908.

hand, no matter how profound these effects have been, no one has obtained focal irritative and paralytic phenomena of the brain such as occur commonly in cerebral air embolism. In this connection it is to be emphasized that in the lung inflation phenomenon of Johnson and Luckhardt the cerebral symptoms were shown to be the result of ischemia of the brain and without relation to the vagal reflex.[38] Disregarding these facts, two extreme and opposite views are held as to the cause of these obscure cases of sudden collapse following instrumentation of the lung. The majority of authors, as Forlanini,[4] Saugmann[40] and Stivelman,[3] diagnose pleural reflex and pay little or no attention to the possibility of air embolism, while others, notably Brauer,[28] Wever[29] and Schlaepfer,[22] as consistently ascribe the condition to air embolism.

All characteristic symptoms that have been noted in this form of air embolism failed when the subject was under general anesthesia or when the air entered rapidly and in large amounts, since no opportunity was given for evidence of involvement of the brain. The picture was simply that of sudden heart and respiratory failure.

The diagnosis made at autopsy of air embolism from the pulmonary vein has depended on the demonstration of air in the blood stream or of typical cerebral lesions. Both of these could not appear in the same body, since air remains in the vessels during life a few minutes or hours only and the degenerative changes in the brain from embolism develop only after fifteen hours.[30] Thus, patients in whom death occurs between two and fifteen hours after the onset of symptoms are expected not to exhibit at autopsy evidence of air embolism, either in the form of intravascular air or that of secondary changes in the brain. Moreover, very small amounts of air may be lethal in embolism from the pulmonary vein, and even though death occurs at once its demonstration in the peripheral vessels is difficult. Use of the roentgen rays has been proposed for diagnosis.[41]

Richter[42] described a technic for the demonstration of air or gas in the vessels at death which has become standard. Each organ is isolated in situ by ligation of the vessel supply, then removed and incised under water. Air escaping from the tissues bubbles up plainly. The heart is managed somewhat more simply, for ligation and removal is dispensed with. The pericardium is opened and held suspended to serve as the dish for water submersion. Objection has been raised to this method as laborious and misleading, for the air may be withheld in the vessels by clots and fail to bubble forth, and the water quickly

40. Saugmann, C.: Beitr. z. Klin. d. Tuberk. **31**:571, 1914.

41. Baum, F.: Am. Med. **33**:271, 1927.

42. Richter, M.: Gerichtsärztliche Diagnostik und Technik, Leipzig, S. Hirzel, 1905.

becomes bloody and obscures the tissues. Moreover, direct observation of the vessels serves to detect even very small amounts of air, since the smaller arterioles are translucent enough to show air bubbles distinctly and the air in larger vessels, heart, cavae and aorta, is present in the form of froth and escapes as such plainly when the lumen is opened.

It is well known that little significance can be placed on finding air bubbles in the cerebral vessels at autopsy, unless great care has been taken in exposing the brain. In lifting off the skull cap, as it is routinely carried out, cortical vessels are stretched and ruptured and air is sucked from the atmosphere into their lumina.

Differentiation at autopsy of the type of air embolism has depended on three things. 1. The vessel that served as portal of entry is sought. 2. The distribution of the air is determined, the fact being borne in mind that the lesser circulation acts as an effectual barrier to air bubbles. Thus, if air was found in the left side of the heart or the peripheral arteries, the case was one of embolism from the pulmonary vein; if only in the large veins, right side of the heart and pulmonary arteries, it was embolism from a peripheral vein. One exception has pertained to this; a patent foramen ovale may allow air to pass from the right to the left side of the heart and differentiation is prevented. 3. The typical cerebral degenerative lesions are sought for and indicate the pulmonary vein type of embolism, unless there is a patent foramen ovale.

It has been emphasized that fallacious conclusions may result from the presence of putrefactive gases in the blood at autopsy. Dyrenfurth [43] found by actual measurement that within twenty-four hours amounts of gas up to 0.25 cc. may be present in the heart cavity, and that this may increase during the next few days to 4 cc. In air embolism from a peripheral vein there was regularly as much as 7 cc., but this is probably too high for embolism from the pulmonary vein, where smaller amounts are lethal. Dyrenfurth [44] devised a method for the qualitative test of these gases, to rule out the putrefactive. Simmonds [45] recommended culture of the heart blood for the presence of gas-forming organisms, for the same purpose.

Prognosis has been uncertain. Usually, the return of consciousness has indicated improvement leading to recovery, but in some cases consciousness has been recovered only for relapse to occur. In recovery after pronounced symptoms, focal paralyses lasting as long as six months have been seen.[46]

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43. Dyrenfurth, F.: Med. Klin. **22**:807, 1926.
44. Dyrenfurth, F.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:727, 1926.
45. Simmonds, M.: München. med. Wchnschr. **62**:662, 1915.
46. Head, J.: Personal communication to the authors.

EXPERIMENTAL WORK

Diagnosis.—A characteristic sign of air embolism from the pulmonary vein, noted practically always in these experiments, was immediate elevation of the arterial blood pressure. The most frequent degree of rise was from 30 to 40 mm. of mercury, but often the initial pressure was more than doubled. The elevation was maintained as long as air continued to be injected and usually also for a minute or two afterward. Even exceedingly small amounts of air produced detectable hypertension. In air embolism from the peripheral vein, on the other hand, initial depression of the blood pressure is the rule. These opposite effects are illustrated in the following experiment.

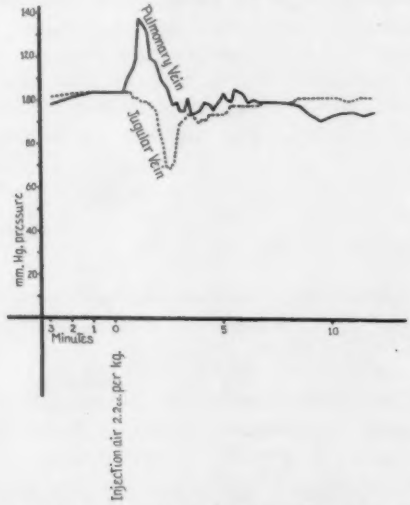

FIG. 10 (dog 6).—Injection of air into the pulmonary vein, followed in thirty minutes by the injection of air into the jugular vein (graphs superimposed).

Dog 6, weighing 8.4 Kg., was fitted with cannulas in both pulmonary and jugular veins. The femoral artery was connected to a mercury manometer and the normal blood pressure level was recorded. Then a small amount of air (2.2 cc. per kilogram) was injected into the pulmonary vein and the blood pressure reaction noted. Forty-five minutes later, when the pressure was again at a normal level, the same amount was injected into the jugular vein, and the reaction again noted.

The two blood pressure curves thus obtained are compared in figure 10 by superimposition. One is seen to be the reverse of the other.

A second characteristic sign of air embolism from the pulmonary vein is elicited as follows: A stab cut is made through the skin of a part of the body that is uppermost and bleeding is produced. Bubbles of air will stream out distinctly with the blood. The test should be made within fifteen minutes after embolism.

Prognosis.—Prognosis in air embolism from the pulmonary vein in the dog was possible within certain limits: 1. The severity of the symptoms depended in general on the amount of air entering the circulation. 2. Primary respiratory failure was looked for only within the first ten to fifteen minutes; primary heart failure, within half an hour. 3. Unconsciousness, when continued longer than half an hour, indicated serious cerebral involvement.

CLINICAL CASES

Case 2 illustrates the use of the blood pressure reaction in the diagnosis of air embolism in man.

CASE 2.—A white woman, aged 51, presented an illness of seven months' duration. The onset was sudden, with chills, fever and pain in the left side of the chest. Cough developed and fever continued for three weeks. There had been continuous cough and intermittent periods of fever since then. There was 250 cc. of foul sputum daily, which was negative for tubercle bacillus. A moderate loss of weight and strength occurred. The diagnosis was chronic abscess of the left lung.

The patient was admitted to University of Iowa Hospital, surgical service. Iodization of the bronchial tree showed a large filling in the center of the left lung, extending laterally to within 2 cm. of the pleura. This was interpreted as an abscess cavity.

On two occasions attempts were made to reach the abscess with an exploratory needle, without success. The third attempt was as follows: With the patient under local anesthesia, the third rib was resected in the anterior axillary line, which was a point shown by fluoroscopy to overly the abscess closely. The pleura was found free, and the wound was packed with gauze to produce adhesions. Four days later, the pack was removed and exploration was performed without anesthesia, the patient sitting semi-erect. A large hypodermic needle, attached to a syringe, was passed perpendicularly through the rib bed into the lung. The parenchyma was found to be tough. Nothing could be aspirated, except that at one point blood was freely drawn and at another air. The puncture was repeated, and at a depth of 5 cm. the patient started to cough. The needle was withdrawn. She raised a little bright frothy blood and continued to cough urgently. She experienced a prickling sensation over the body surface and became unable to speak. Dyspnea developed and, at about one minute, unconsciousness. The pulse rate was 66, and was slightly irregular. The color was somewhat cyanotic. At about ten minutes (accurate time is not kept at such emergencies) the blood pressure was taken and found to be 180 systolic and 80 diastolic; at twenty minutes, 162 systolic and 76 diastolic; at thirty minutes, 152 systolic and 70 diastolic; at forty minutes, 140 systolic and 68 diastolic; at fifty minutes, 130 systolic and 65 diastolic, and seventy-five minutes, 125 systolic and 65 diastolic. Consciousness returned at thirty minutes and with it speech; at this time it was noted that the entire left side of the body was paralyzed and with hyperactive tendon reflexes. There was no anesthesia. The eyegrounds were normal. At forty-five minutes, the paralysis began to disappear and cleared at one hour. A sensation of heaviness persisted in that side of the body. Dyspnea gradually disappeared. After one and one-half hours the condition was normal, except for the pulse rate, which was 120.

It was thought that air embolism from the pulmonary vein was the cause of the condition, since: 1. Needle puncture in a sclerotic lung is known (case 1) to be capable of producing a bronchovenous fistula, and such a communication permits air to be inspired into the circulation. Here a bronchus and blood vessel are known to have been pierced in a sclerotic lung. 2. During the height of the reaction the blood pressure was found markedly elevated, and in no other form of sudden collapse, save cerebral hemorrhage, is this seen. 3. The symptoms were chiefly those of transient cerebral dysfunction characteristic of air embolism of the brain.

DEDUCTIONS

The diagnosis of air embolism from the pulmonary vein is assisted by two phenomena, readily elicited:

1. Initial elevation of the blood pressure: In the dog, this lasts as long as air continues to enter the circulation and heart action is maintained. Even very small amounts of air produce noticeable elevation. In man, the reaction is described, and here the elevation was maintained about one hour. The presence of this phenomenon in cases of sudden collapse with instrumentation of the lung rules out air embolism from a peripheral vein, pleural and vagal reflex, hemorrhage and traumatic shock. Its transiency rules out cerebral hemorrhage.

2. "Air bleeding": In air embolism from the pulmonary vein, the peripheral capillaries in the upper parts of the body contain bubbles of air, and these flow plainly out with the blood from a wound. A small stab incision serves to demonstrate this. The phenomenon is pathognomonic.

Prognosis is difficult; it depends on appreciation of the amount of air embolus, severity of symptoms and the time interval.

PREVENTION

Measures to insure against air or gas embolism during the administration of artificial pneumothora, particularly at the initial filling, have eliminated much of the danger. Thus, there is the incision method of Brauer,[47] employment of a blunt needle, manometer control, etc. The accident occasionally takes place, however, even in the best hands.

During the irrigation and probing of pleural fistulas, it has been advocated [48] that no injury, either by direct trauma or by stretching, be inflicted on the pleural surface or pleural adhesions. Instances of shock following such procedures have been accompanied by bleeding as evidence of damage to vessels within the sinus.

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47. Brauer, L., and Spengler, L.: Beitr. z. Klin. d. Tuberk. **14**:419, 1909.

48. Schlaepfer, K.: Surg. Gynec. Obst. **37**:510, 1923.

Spontaneous suction by a pulmonary (or other) vein of air from the outer atmosphere is prevented with certainty by causing the patient to breathe under positive pressure at the time, as demonstrated by Tiegel in 1907.[49] The principle of the apparatus necessary for this purpose is illustrated in figure 11.

EXPERIMENTAL WORK

Various measures that might be expected to prevent spontaneous air embolism from the pulmonary vein were tested in the dog, (1) under the conditions of external venous fistula and (2) under conditions of bronchovenous fistula.

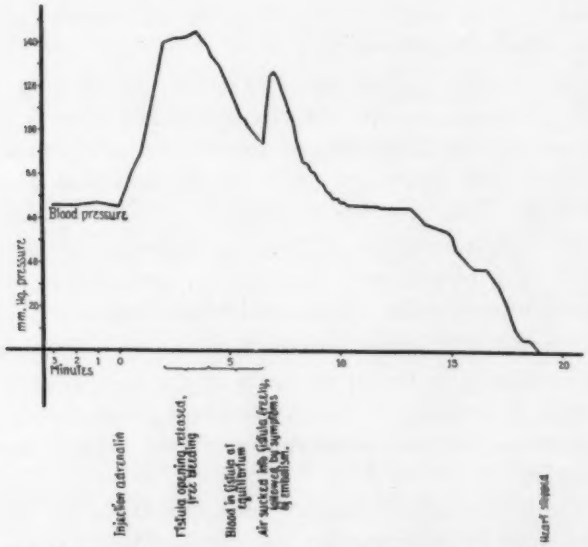

FIG. 11 (dog 50).—Pulmonary vein fistula; temporary protection against air suction by the injection of epinephrine.

External Fistula.—(*a*) Positive Pressure Breathing, Two Dogs: Dog 49, weighing 8.5 Kg., was anesthetized and fitted with a pulmonary vein cannula. Placed in the horizontal position, positive pressure breathing was applied.

At 20 cm. of water pressure, the cannula was opened. The blood from the vein flowed freely out, both in inspiration and in expiration.

At 17 cm. of water pressure, the bleeding was less free.

At 14 cm. of water pressure, bleeding occurred during expiration, and the column of fluid in the cannula remained stationary in inspiration. At 11 cm., the column of fluid was stationary in expiration and dropped toward the vein slightly in inspiration.

At 8 cm., the fluid meniscus appeared above the surface of the chest in expiration and dropped below in inspiration.

At 5 cm., the fluid remained always below the surface of the chest but embolism did not occur.

49. Tiegel, M.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **3**:789, 1907.

At 3 cm., air was drawn freely through the cannula, and the animal died of air embolism.

(*b*) Intravenous Injection of Epinephrine, Four Dogs: Dog 50, weighing 5.8 Kg., was placed under general anesthesia, in the horizontal position, and was fitted with a pulmonary vein cannula and a femoral blood pressure recording apparatus. The normal pressure was recorded, and then 0.5 cc. of epinephrine hydrochloride was injected intravenously (fig. 11).

At injection, the blood pressure started to rise.

At two minutes, when the pressure was 74 mm. of mercury above normal, the cannula was opened and found to bleed freely.

The pressure continued to rise and then fell gradually with constant tendency to bleed from the cannula.

At four minutes ten seconds, when the pressure was 72 mm. of mercury above normal, equilibrium was reached. As the pressure fell further the meniscus in

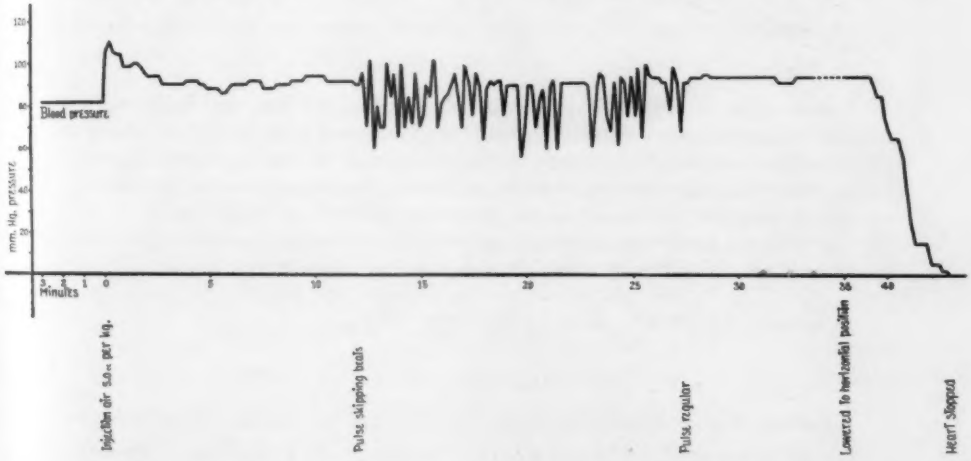

FIG. 12 (dog 111).—Injection of air into the pulmonary vein, with the dog in the head-down position. Illustrating the fatal effect of resuming the horizontal position too soon.

the cannula dropped, and at six minutes thirty seconds, at 28 mm. of mercury elevation, there was sucking of air into the vein, and the dog died from embolism.

In other dogs, the effect was similar, although the blood pressure values were different in each case. Ephedrine was found to act in the same manner.

Bronchovenous Fistula.—(*a*) Positive Pressure Breathing, One Dog: In dog 51, weighing 6.9 Kg., while under general anesthesia, a bronchovenous fistula was created as in dog 1 (section on etiology) and the communication was kept blocked at first by clamping the U-tube. Positive pressure breathing was applied. At 10 cm. of water pressure, the clamp was removed and patency of the fistula was established. Air passed immediately from bronchus to vein, and the dog died.

(*b*) Negative Pressure Breathing, One Dog: Dog 52, weighing 7.5 Kg., was treated in a similar manner to dog 51, except that negative pressure breathing

was administered. At 24 cm. of water pressure, the clamp was removed from the U-tube. Air passed rapidly from the bronchus to the vein. The dog died.

(*c*) Intravenous Injection of Epinephrine, Three Dogs: Dog 53, weighing 9.2 Kg., was fitted with a bronchovenous cannula and a femoral blood pressure recording apparatus. The normal pressure was determined and then 0.5 cc. of epinephrine hydrochloride was injected intravenously.

At injection, the blood pressure began to rise.

After one minute and fifty seconds, with the pressure 56 mm. of mercury above normal, the U-tube was released. The venous blood flowed quickly toward the bronchus.

The pressure continued to rise and then fell gradually, with a constant tendency to bleed from the vein.

After four minutes, the pressure reached 14 mm. of mercury above normal and air was drawn with each inspiration from bronchus to vein, with death.

A similar, transient protection against embolism was seen in the other dogs.

Bronchus Block, Three Dogs: Dog 54, weighing 10 Kg., was fitted with a bronchovenous cannula. A small rubber bag connected with a rubber tube was introduced by bronchoscope into the primary bronchus on the side of the cannula. By inflating the bag suddenly during expiration, the bronchus was blocked and a negative pressure established in the peripheral bronchi in inspiration.

The bronchovenous cannula was released; no air passed into the vein. The bronchus block was released; fatal air embolism immediately took place.

A similar result was seen in the other dogs.

DEDUCTIONS

Spontaneous air embolism from an external fistula of the pulmonary vein was prevented in dogs by two means: (1) Positive pressure breathing (Tiegel), with pressure as low as 5 cm. of water; pressures above 14 cm. of water caused the vein to bleed. (2) The intravenous injection of epinephrine or ephedrine; the protection lasted only while the blood pressure remained above certain levels, which was only a few minutes. Accompanying this was a tendency to bleed from the vein.

Spontaneous embolism from a bronchovenous fistula in dogs was prevented by two means: (1) The intravenous injection of epinephrine or ephedrine; the effects were the same as in external fistula. (2) Bronchial block; protection lasted as long as the block was maintained, and without tendency to bleed from the vein. The use of positive pressure or negative pressure breathing afforded no protection but rather encouraged embolism.

TREATMENT

Consistent benefit in air embolism from the pulmonary vein has not been obtained experimentally or clinically by any form of treatment. Cardiorespiratory stimulants and intracardiac injections of epinephrine

have had no effect. Gundermann [19] exposed the heart in dogs and aspirated and massaged the ventricle but could not rescue any one. He explained his failure by indicating the cause of heart failure as myocardial ischemia, necessarily resistant to any artificial stimulant short of reestablishment of the coronary circulation. Reyer and Kohl [50] suggested that the person's head be lowered after embolism, in order to bring additional blood to the brain, but this has not proved of assistance.

EXPERIMENTAL WORK

Two measures appeared of likely value in treatment, as indicated by the aforementioned experimental observations, i.e., artificial respiration and the use of the head-down position preliminary to air embolism.

Artificial Respiration, Seven Dogs.—These experiments were carried out in the following manner:

Each dog was placed under general anesthesia in the horizontal position, and a pulmonary vein cannula was inserted. Continuous intratracheal insufflation of air, according to the original principle of Meltzer and Auer,[51] was instituted, and then a measured dose of air was injected into the pulmonary vein at a rate of 25 cc. per minute. The outcome was noted, whether by death or by recovery at four hours. The amounts of air were varied, to determine the maximum tolerance dose.

The maximum tolerance dose was 1.5 cc. per kilogram, which is the same as that found without artificial respiration in this position.

Vertical Position, Head Down, Thirty-two Dogs.—Experiments have been described in the section on tolerance (fig. 9) which indicate that, when the dog is in a vertical position, head down, the maximum tolerance dose is 3.3 cc. per kilogram of body weight, or two times that in the horizontal position.

Vertical Position, Head Down, Plus Artificial Respiration, Fifteen Dogs.—The artificial respiration was combined with the head-down position, described in the two previous experiments. The maximum tolerance dose for air injected into the pulmonary vein was found to be 5 cc. per kilogram of body weight or 50 per cent greater than with the head-down position alone.

This increased tolerance to air embolism was obtained only when artificial respiration was maintained at least one-half hour and when the position was held for one hour or more. The latter requirement is emphasized by experiment:

Dog 111, weighing 12 Kg., under general anesthesia, was placed in a head-down position and given 5 cc. of air per kilogram of body weight into the pulmonary vein, and the reaction was noted (fig. 12).

At thirty-eight minutes, recovery from the embolism seemed complete. The anesthetic had been discontinued and the dog had regained consciousness. The

50. Reyer, G. W., and Kohl, H. W.: Air Embolism Complicating Thoracic Surgery, J. A. M. A. **87**:1626 (Nov. 13) 1926.

51. Meltzer, S., and Auer, J.: J. Exper. Med. **11**:622, 1909.

table was lowered to the horizontal position. Immediately, the blood pressure rose slightly and then dropped steadily to 0 at forty-seven minutes.

At autopsy, it was found that air that had accumulated in the large trunk and the arteries of the hind legs had passed backward against the blood stream, ascended the aorta and reached the branches leading to the head and the coronary arteries. This retrograde embolism had obviously occurred at the time of change of the animal's position.

This occurrence of retrograde embolism on change of body position was demonstrated in two other dogs by means of air traps inserted in various vessels.

DEDUCTIONS

Treatment for air embolism from the pulmonary vein by artificial respiration (intratracheal insufflation of Meltzer and Auer) is of assistance only when the animal has been placed in a steep, head-down position before the onset of embolism. The tolerance for air embolus

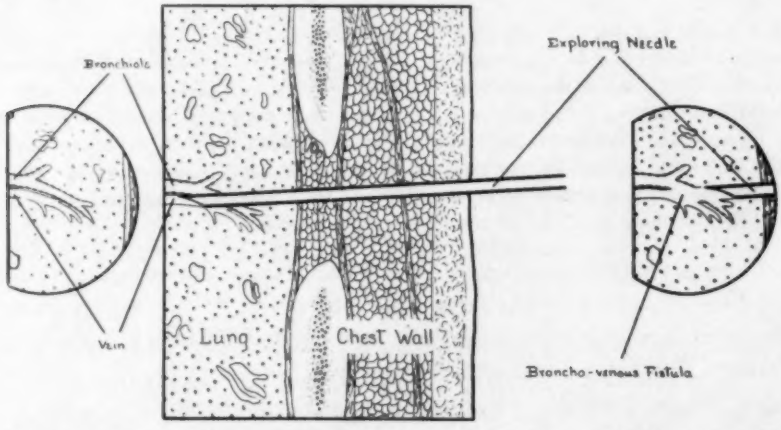

FIG. 13.—Cross-section of the thoracic wall and underlying lung with exploring needle in place. Illustrating the mode of formation of a bronchovenous fistula by needle puncture.

is then 5 cc. per kilogram of body weight, which is distinctly greater than under any other circumstances tested and is ten times as great as in the most susceptible circumstance, i.e., with the head up.

Artificial respiration must be continued for half an hour and the head-down posture for one hour in order to obtain the beneficial effects.

COMMENT

Air embolism from bronchovenous fistula is a complication demanding consideration in exploratory needle puncture of the lung, judging from the evidence of cases 1 and 2. In the parenchyma of the lungs the pulmonary veins lie in close proximity to bronchi, and transfixion of both vein and accompanying bronchus by the needle leaves defects in their walls at adjacent points (fig. 13). If, then, the parenchyma is

consolidated and inelastic, as it frequently is when such exploration is made, the pathway may remain temporarily patent. Likewise, a bronchovenous fistula may form readily in the case of a pulmonary cavity containing a vein in its wall, where a tangential needle thrust could tear the thin partition separating the lumen of the vein from the cavity. Given a patent bronchovenous communication, the vein becomes a branch of the bronchial tree and receives air during inspiration as voluminously as does any bronchial branch of like caliber. Here the person literally breathes into his circulation. The autopsy in case 1 revealed hundreds of cubic centimeters of air in the blood vessels. Such a mechanism may account for many of the obscure instances of sudden collapse following thoracentesis.

The extreme points of view commonly held as to the cause of these obscure complications following lung instrumentation, ascribing it entirely either to air embolism or to pleural reflex, are not justified by the available clinical and experimental evidence. That both entities exist as such and may occur in man and animals is established beyond reasonable doubt, as we have outlined, and differentiation must be made in diagnosing each case. Symptoms of irritation or paralysis of the higher brain centers point to embolism, but in the presence of cardiovascular symptoms alone either of the causes may be in play.

Differential diagnosis is assisted greatly by examination for one or both of two phenomena, i.e., sudden blood pressure alteration and "air bleeding." Marked depression of the blood pressure is seen in pleural reflex and other forms of shock, while elevation is characteristic of air embolism from the pulmonary veins. "Air bleeding" is, of course, pathognomonic of the latter. These signs are obtainable with instruments usually at hand and with no unusual amount of skill.

Air embolism from the pulmonary vein in its various forms is preventable. When there is a possibility of embolism occurring from external fistula of the vein, the use of positive pressure breathing may be relied on to eliminate the negative intrathoracic pressure and the capacity of the thoracic veins for suction. The Tiegel method (fig. 14) is perhaps the best, being simple and well tolerated by the conscious patient. Its principal advantage over other apparatus of the sort is the freely open breathing outlet, for submergence under water is used to procure pressure and there is no choking sensation produced as occurs with the spring valve devices, which elevate the pressure within the mask by obstruction to the outlet. Moreover, the water submersion principle sets the pressure desired and insures against accidental overdistention of the lungs. The pressure used is slight, from 8 to 10 cm. of water.

When there is a possibility of embolism from bronchovenous fistula, certain and controllable means of prevention are obtained only by

blocking the bronchus leading to the affected lung during the operation. The technic for this in man has not been developed but should be comparatively simple and without necessity of bronchoscopy. A fine catheter fitted at the end with a small rubber bag may be passed through the anesthetized larynx and into the bronchus under fluroscopic control, as in the Iglauer [52] method for iodization. The use of epinephrine to raise the pulmonary intravenous pressure prevents spontaneous suction by the veins but the effect is too transient to be practicable.

The treatment for air embolism is of little avail. The embolized vital centers cannot be well reached by medication and there is no way of removing the air lodged in the vessels. Anoxemia may be prevented and distinct benefit obtained by the use of artificial respiration, as carried

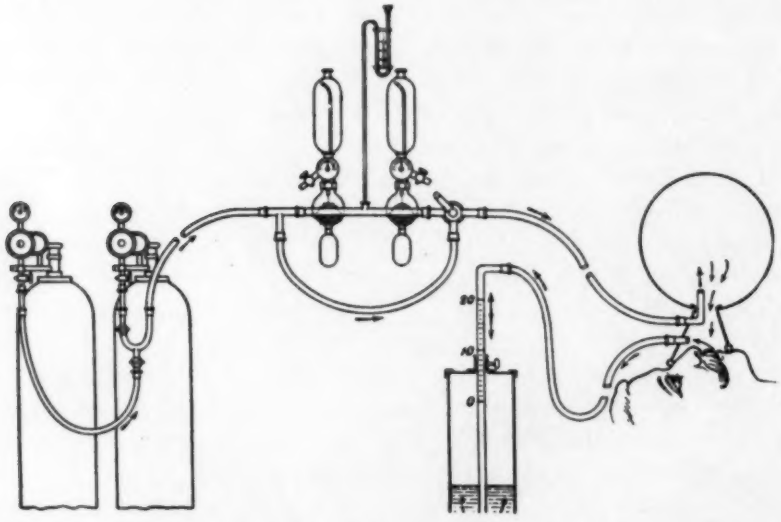

FIG. 14.—Positive pressure breathing apparatus applied to man, according to Tiegel. The air is supplied by tanks to the breathing mask and bag, and the exhaust air is carried out by a tube under water. The depth of the outlet under water determines the pressure breathed.

out in the experiments reported; this is not applicable to clinical experience, as only the principle of continuous intratracheal insufflation is desirable. Any procedure for administering artificial respiration which entails increasing the chest movements is likely to add to the air embolism and should be avoided. Once air embolism has occurred, it is of no benefit to institute the Trendelenberg position. The patient should be allowed to lie in the original position quietly and fight his own battle.

52. Iglauer, S.: Injected Iodized Oil in Roentgen-Ray Diagnoses of Laryngeal, Tracheal and Broncho-Pulmonary Conditions, J. A. M. A. **86**:1897 (June 19) 1926.

When an operation is contemplated in which there is a possibility of air embolism occurring and when certain means of prevention are not at hand the following procedure is advocated:

During the stage of the operation in which embolism is likely to occur, the patient is placed in a steep Trendelenberg position. The blood pressure is taken every minute or so, to warn of complications and indicate immediate interruption of the operation. If a sudden, marked elevation points to embolism, the diagnosis may be confirmed by eliciting "air bleeding," and the patient must then be maintained in the head-down posture for about two hours, to obviate shifting of the air to other parts of the body (coronary and cerebral vessels). Oxygen may be administered with a tent or other efficient passive methods.

SUMMARY

The subject of air embolism from the pulmonary vein is considered in this paper as to etiology, distribution of the air in the circulation, physiologic reaction, tolerance, cause of death, diagnosis, prognosis, prevention and treatment. Under each of these captions is given a review of the present knowledge and original clinical and experimental observations and deductions.

Particular emphasis is placed on the following conclusions:

1. Bronchovenous fistula may be produced by simple thoracentesis and may form a portal of entry for air into the pulmonary veins.

2. Gravity is a determining factor distributing air in the blood circulation.

3. Embolism of the heart (coronary) and brain are the vital effects. The position of the animal determines which of these are primary in a given case.

4. Tolerance for embolism is greatest when the head of the animal is well depressed and least with the head up.

5. Diagnosis is aided by two characteristic and easily elicited signs, i.e., elevation of the initial blood pressure and "air bleeding."

6. Prevention is certain by employing positive pressure breathing, when an external venous fistula is present, or by bronchial block, when a bronchovenous fistula exists.

7. Treatment, although effective under ideal circumstances, is not practical.

EXPERIMENTAL PEPTIC ULCER*

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REVIEW OF THE LITERATURE

A consideration of the numerous methods of procedure used in the experimental study of peptic ulcer shows that experimental ulcers may be grouped under a few general headings: (1) resulting from a deficient blood supply to the gastric mucosa; (2) produced by the action of bacteria; (3) resulting from the action of toxic agents; (4) resulting from trophic and glandular disturbances, and (5) produced by the action of the digestive juices.

Prior to Virchow's time, experimental studies of the problem had not been carried out. Indeed, a clear recognition of peptic ulcer as a distinct pathologic and clinical entity was not achieved until comparatively late in the progress of medical science. Galen, Celsus and other ancient investigators, presented vague and doubtful references to the ulcer in their descriptions of passia cardiaca, hematemesis and melena. The post-mortem examinations of the sixteenth century, stimulated by the general revival of original investigation, resulted in many descriptions of ulcer and cicatrices of the stomach. Bonetus (1679) published in the *Sepulchretum* one of the earliest recorded cases of perforating ulcer, which was observed by John Bauhin; other cases were described in the next century by Donatus, Courtial, Littre, Shenck and Morgagni. Matthew Baillie (1793) published the first accurate study of the anatomic peculiarities of ulcer; he republished the work later with three engravings and clinical data, but it had little influence on contemporary medical thought. A valuable description of the clinical syndrome, including nearly all the symptoms now recognized as characteristic of the malady, was published by John Abercrombie (1824). Cruveilhier (1829-1835) was the first to differentiate clearly ulcer of the stomach, carcinoma of the stomach and ordinary gastritis. He gave a clear anatomic and clinical description of the disease suggesting, as its primary cause, preceding gastritis. He anticipated the modern view expressed by Nauwerck [1] and supported by the studies of Konjetzny [2]

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the degree of Doctor of Philosophy in Surgery.

1. Nauwerck, C.: Mykotisch-peptisches Magengeschwür, München. med. Wchnschr. **42**:876 and 908, 1895.

2. Konjetzny, G. E.: Entzündliche Genese des Magen-Duodenalgeschwürs, Arch. f. Verduungskr. **36**:189, 1925.

and others, that gastritis might be the primary condition and the basis of the formation of ulcer. The other modern view, that hemorrhagic erosions establish the basis for a subsequent ulcerative process, was first expressed by Rokitansky [3] in his description of seventy-nine cases.

VASCULAR SUPPLY

Historically, the first groping toward an explanation of the cause of ulcer was the concept of vascular insufficiency. Theory preceded experiment and outlined its development. Virchow [4] announced his theory that vascular infarction was the primary etiologic factor in causing the formation of ulcer in the stomach. He visualized an ulcer as local ischemic necrosis induced by the embolic occlusion of a vessel; this vascular lesion mechanically removed the alkalinizing influence of the blood, and permitted the local destruction of the gastric wall by the corroding hydrochloric acid. The typical conical shape of the ulcer and its eccentric perforation of the serous coat depended, he believed, on the conical distribution of the tuft of vessels arising from the occluded eccentric arterial rootlet. Janeway [5] presented to the New York Pathological Society a clinical case of ulcer with a fibrinous plug in a branch of the gastro-epiploic artery leading to the ulcer; a source of the plug was not found. Cohnheim,[6] in reviewing the old authorities, recalled Klebs' [7] belief that local ischemia due to spastic contraction of the arteries furnished the basis for ulceration; that Virchow attributed it to disease of the vessels, particularly embolic occlusion; that Günsburg [7] thought impediments to the escape of venous blood acted as a cause; that Key [7] held that mechanical hyperemia, caused by abnormal contraction of the gastric musculature, might cause local hemorrhage leading to the formation of the ulcer, and that Quincke believed general anemia to be a significant factor.

Embolus.—Experimental study of these hypotheses was first attempted by Panum [8] and Cohnheim.[6] Accepting Virchow's theory, Panum injected an emulsion of wax into the central end of the femoral artery of dogs; multiple small hemorrhagic infarcts and ulcers formed in

3. Rokitansky, Carl: A Manual of Pathological Anatomy, London, Sydenham Society, 1849, vol. 2, p. 31.

4. Virchow, R.: Historisches, kritisches und positives zur Lehre der Unterleibsaffektionen, Virchows Arch. f. path. Anat. **5**:362, 1853.

5. Janeway, E. G.: The Cause of Perforating Ulcer of Stomach, M. Rec. **6**:427, 1871-1872.

6. Cohnheim, J.: Lectures on General Pathology, London, The New Sydenham Society, 1890, vol. 3, p. 875.

7. Klebs; Günsburg, and Key, quoted by Cohnheim: Lectures on General Pathology, London, The New Sydenham Society, 1890.

8. Panum, P. L.: Experimentelle Beiträge zur Lehre von der Embolie, Virchows Arch. f. path. Anat **25**:433, 1862.

the stomach. However, the dogs died within twenty-four hours from widely disseminated emboli, so that the ultimate course of these ulcers was a matter of conjecture. Cohnheim injected lead chromate suspension into the gastric branches of the splenic artery, which caused large ulcers with precipitous walls on the second day; several small ulcers persisted into the second week, and complete healing occurred in the third week. In subsequent studies, Payr [9] and Grossi [10] injected a suspension of bismuth subgallate in sterile water into the gastric veins of twenty dogs, which caused submucous hemorrhage and acute ulcerations. Chessine and Feldmann,[11] injecting a 10 per cent emulsion of bismuth subgallate, produced infarcts of the mucosa, but only when they induced concurrent secondary anemia (hemoglobin 40 per cent) by the intravenous injection of chloral hydrate and phenylhydrazine; all ulcers were healed in thirty days, one showing cicatrization. Ivy [12] used finely divided emboli of animal charcoal, which gave negative results after injection into the gastro-epiploic vessels; however, using lead chromate and pigments, he produced ulcers which he interpreted as of toxic origin. Greggio [13] and Bolton [14] quoted other experiments on the injection of emboli which produced variable results: Sapiejko used lycopodium; Kobayashi and Nauverck used mycotic emboli; Vigliani used a "coagulating substance"; Rosenbach and Exner injected liquid paraffin and cultures of staphylococci into the gastro-epiploics; Shridde used fat emboli; Klebs and Welti used emboli formed from blood corpuscles and pigment granules, and Prevost and Cottard introduced tobacco into the aorta of a rabbit. Wilkie,[15] interpreting the hematemesis that occasionally follows abdominal operations as due to retrograde emboli from omental thrombosis, injected solid particles of sterile oil into an omental vein. These particles impacting in the smaller venous branches caused submucous erosions and definite infarctions of the stomach, with associated infarcts of the spleen and liver. Greggio cited other studies with the

9. Payr, Erwin: Experimente über Magenveränderungen als Folge von Thrombose und Embolie im Pfortadergebiete, Arch. f. klin. Chir. **84**:799, 1907.

10. Grossi, V.: Recherches expérimentales sur la production de l'ulcère gastrique par troubles circulatoires, J. de chir. **17**:502, 1921.

11. Chessine, V. R., and Feldmann, A. S.: Étude sur l'ulcère expérimental de l'estomac, J. de chir. **10**:65, 1913.

12. Ivy, A. C.: Studies on the Experimental Gastric and Duodenal Ulcer, Am. J. Physiol. **49**:143, 1919-1920; Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920; Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920.

13. Greggio, Ettore: Des ulcères gastro-duodénaux, Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

14. Bolton, Charles: Ulcer of the Stomach, London, Edward Arnold, 1913, p. 386.

15. Wilkie, D. P. D.: Retrograde Venous Embolism as a Cause of Gastric Ulcer, J. Path. & Bact. **15**:355, 1911.

omentum: Sapiejko burned it, and Eiselberg, Friedlich, Pavy, Schiff, Matthes and Gibelli ligated it, all with uncertain or negative results.

Ligation of Vessels.—These unsatisfactory methods of study were supplanted by ligation of vessels. Litthauer [16] found the anastomosis of vessels so free that a third of the blood supply to the stomach could be cut off without the formation of ulcer. Turck [17] ligated all the vessels of the stomach and produced erosions. Fenwick [18] failed to produce lesions by ligating only a few veins, but by tying most of them and injecting the portal vein with tincture of perchloride of iron, he produced hemorrhages and ulcers. Bolton quoted Mueller, Pavy, Roth and Litten as obtaining negative results from ligature of the larger arteries. Interference with the blood supply associated with injury to the mucosa was studied by Litthauer; he tied all the vessels in a given portion of the stomach, excised a piece of mucosa from that area and fed dilute hydrochloric acid; he procured ulcers in only two of eight experiments. Clairmont,[19] Greggio [13] and Matthes [20] performed similar experiments, cauterizing the borders of the ulcer with hydrochloric acid, and found that ulcers formed easily in the pyloric region but not in the cardiac region. Yano [21] found that whereas ligation of the gastro-epiploic arteries had no effect on the fundic mucosa, ligation of the gastric or pyloric artery led, as shown by intravenous injections of dye, to localized nutritional disturbances in the "Magenstrasse" of Waldeyer and Aschoff.

The studies on vascular occlusion in relation to the formation of ulcer suggested to Berlet [22] a possible relationship between the anatomic distribution of the vessels and the site of greatest ulcer incidence. He injected the gastric arteries of twenty cadavers with a solution of gelatin containing red lead. Roentgen studies demonstrated that the blood

16. Litthauer, Max: Experimentelle Untersuchungen zur Pathogenese des runden Magengeschwürs, Arch. f. path. Anat. u. Physiol. **95**:317, 1909; Recherches expérimentales sur la pathogénie de l'ulcère rond stomacal, J. de chir. **2**:424, 1909.

17. Turck, F. B.: Preliminary Report on Ulcer of the Stomach: Pathogenesis and Pathology, Tr. Path. Soc. Chicago **6**:439, 1903-1906.

18. Fenwick, quoted by Bolton: Ulcer of the Stomach, London, Edward Arnold, 1913.

19. Clairmont, Paul: Ueber das experimentelle erzeugte Ulcus ventriculi und seine Heilung durch die Gastroenterostomie, Arch. f. klin. Chir. **86**:1, 1908.

20. Matthes, Max: Untersuchungen über die Pathogenese des Ulcus rotundum ventriculi und über den Einfluss von Verdauungsenzym auf lebendes und todtes Gewebe, Beitr. z. path. Anat. **13**:309, 1893.

21. Yano, quoted by Aschoff: Lectures on Pathology, New York, Paul B. Hoeber Company, 1924.

22. Berlet, K.: Ueber die Arterien des menchlichen Magens und ihre Beziehungen zur Aetiologie und Pathogenese des Mageneschwürs, Frankfurt: Ztschr. f. Path. **30**:472, 1924.

supply to the pyloric region was much more sparse than that to the other parts of the stomach. He inferred that this predisposed the region to circulatory disturbances, rendering it much less capable of developing compensatory collateral circulation. Reeves [23] found that the vessels in the submucosa of the lesser curvature are smaller and longer, without as free anastomosis as in the other regions of the stomach; also that they are tortuous, with constantly increasing resistance to the blood stream. In the first part of the duodenum there are relatively few vessels in comparison with other parts of the duodenum. He concluded that these vessels are more prone to occlusion by emboli and may play an important part in the production of ulcer by hematogenous infection.

Occlusion of Vessels.—The theory sponsored by von Bergmann,[24] that spastic contraction of the arteries causes local ischemia which is the starting point for digestion by the gastric juice and subsequent ulceration, has met with considerable favor among German investigators. Westphal,[25] trying to prove the spasmogenic theory of Klebs and von Bergmann, injected large subcutaneous doses of pilocarpine, with and without physostigmine, into rabbits. This produced ulcers and erosions which he considered to be the result of spastic muscular contraction due to extreme vagal irritation. His experiments with cats, dogs and guinea-pigs were not so successful. With the stomach of the rabbit exposed, he observed long continued, spasmodically increased peristalsis, followed by cyanosis and pallor; snow-white specks appeared suddenly on the mucosa in which a dark center occurred. The anemic foci he believed to be due to vascular spasm with impoverishment of the blood supply to the mucosa. On the basis of the lesion ranging from hemorrhagic erosions to chronic perforating ulcers, which were produced with pilocarpine, epinephrine and morphine, singly and combined, Nakashima [26] accepted von Bergmann's theory as the most logical explanation of the pathogenesis of ulcer. Underhill and Freiheit [27] made direct observations on the stomach after injecting pilocarpine and epinephrine, from which they concluded that the lesions depended on cyanosis of the stomach and localized areas of anemia, on which the gastric contents exerted

23. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg. Gynec. Obst. **30**:374, 1920.

24. Von Bergmann, G.: Ulcus-Probleme, Jahresk. f. ärztl. Fortbild. **12**:3, 1921.

25. Westphal, K.: Untersuchungen zur Frage der nervösen Entstehung peptischer Ulcera, Deutsches Arch. f. klin. Med. **114**:327, 1914.

26. Nakashima, Yoshisada: Die Pathogenese des Ulcus pepticum ventriculi et duodeni experimentelle Beiträge zu von Bergmanns spasmogener Theorie, Ztschr. f. d. ges. exper. Med. **47**:4, 1925.

27. Underhill, F. D., and Freiheit, J. M.: Effect of Pilocarpine and Epinephrine in Production of Specific Lesions in the Stomach of Rabbits, Arch. Path. **5**:411 (March) 1928.

a destructive action. Hayashi [28] interpreted the ulcerous changes produced by injecting nicotine into guinea-pigs as due to obstruction of the arteries by muscular contraction. Gallagher [29] demonstrated that localized anemia of the duodenal mucosa produced by pressure, if it were maintained for a minimal period of forty minutes, resulted in superficial ulcers. Haeller [30] declared that Westphal's results were not due to gastric spasm, but to disturbances of the circulation and metabolism resulting from severe general intoxication. He believed the lesions to be a result of the toxic action of the drug, as he produced ulcerations with morphine, physostigmine and atropine, which exert a different physiologic effect.

Connor,[31] in a histologic study of peptic ulcers, ascribed the chronicity of ulcer and its failure to heal to thrombosis of the vessels in the surrounding tissue. It is possible that this thrombosis is an effect and not the cause of the local condition, for Mann has reported a thrombotic process from the inflammatory reaction accompanying experimental ulcers. The fact that Morton [32] procured healing of ulcers after gastroenterostomy indicates that the thrombotic element, which would have been unaffected by this surgical procedure, might not have been the essential factor in maintaining chronicity. Konjetzny [2] did not observe thrombosis in the areas of gastritis and duodenitis, which he regarded as the possible basis of the formation of ulcer.

Anemia.—Many investigators have believed that general anemia as well as local vascular insufficiency has some bearing on the production of ulcer. Quincke first suggested this possibility. Zironi [33] produced ulcerations in 80 per cent of animals rendered anemic by the injection of pyrodine after bilateral vagotomy; in the absence of anemia, lesions appeared in only 59 per cent of cases and were neither so deep nor so extensive. Silbermann,[34] Litthauer [16] and Matthes [20] presented evidence

28. Hayashi, Toshii: Experimentelle Beiträge zur Frage der Ulcusentstehung, Ztschr. f. d. ges. exper. Med. **34**:224, 1923.

29. Gallagher, W. J.: Acute Traumatic Ulcers of the Small Intestine, Arch. Surg. **15**:689 (Nov.) 1927.

30. Haeller, S. J.: Untersuchungen zur neurogenen Pathogenese des Ulcus ventriculi pepticum, München. med. Wchnschr. **1**:393, 1920.

31. Connor, C. L.: The Etiology and Pathology of Peptic Ulcer, Boston M. & S. J. **195**:971, 1926.

32. Morton, C. B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer: A Consideration of Etiology; II. A Röntgenologic Study of Experimental Chronic Ulcer; III. Healing of Experimental Peptic Ulcer After Gastro-Enterostomy, Ann. Surg. **85**:207, 1927.

33. Zironi, Giuseppe. Contributo sperimentale alla patogenesi dell' ulcera rotonda dello stomaco, Riforma med. **24**:1046, 1908; Experimenteller Beitrag zur Pathogenese des Ulcus rotundum des Magens, Arch. f. klin. Chir. **91**:662, 1910.

34. Silbermann, quoted by Bolton: Ulcer of the Stomach, London, Edward Arnold, 1913.

to show that anemia and hyperchlorhydria prolonged acute ulcers only to a negligible degree. Turck reported that ulcers occurred in animals simply by keeping them in close confinement until they were debilitated. Gibelli [35] reported negative results after anemia produced by bleeding.

Portal Insufficiency.—Finally, interference with the portal circulation, although of indirect action, has been associated with the formation of ulcer. Mueller [36] and Fenwick,[18] by sudden occlusion of the portal vein, caused hemorrhages of the mucosa and ulcerations, chiefly in the cardiac end of the stomach. Following ligation of the portal vein, Gundermann [37] observed hepatic dysfunction with cerebral, renal and digestive disturbances; hemorrhages and ulcerations occurred in the stomach and duodenum. Payr produced acute ulcers (also certain chronic types) which perforated in three weeks by compression of the portal vein and injections of alcohol and formaldehyde. Turck interrupted the blood supply to the liver and ligated the blood vessels on the lesser curvature of the stomach; this resulted in congestion with hemorrhagic spots and erosions in the stomach. Bollman and Mann [38] reported that in a fairly large percentage of dogs subjected to true Eck fistula and fed with coarse kennel food perforating duodenal ulcers may form after a period of several months.

BACTERIAL RELATIONSHIP

As Virchow's theory of the vascular origin of ulcer had initiated considerable study of the influence of that factor, so Cruveilhier's comparison of peptic ulcer to intestinal typhoid ulcer stimulated investigation of the bacteriologic relationship of ulcer.

Early Experiments.—Lebert (1837), probably stimulated by the contemporary advances in bacteriology, injected pus into the veins of animals, with resulting pyemia and erosions of the gastric mucosa. Cohn (1860) produced similar erosions by the same method. The presence of bacteria in the marginal tissues of ulcer was demonstrated first by Böttcher (1874). Greggio and Bolton reviewed the earliest bacteriologic studies as follows: Lettule (1828) produced gastric lesions by the intravenous injection of *Bacillus pyocyaneus;* so also did Charrin and Ruffer. Wurtz and Leudet used lactic bacillus; Rosenbach and

35. Gibelli, D. C.: Contributo critico sperimentale all'esiologie dell' ulcera gastrica in rapporto coi traumi, Arch. internat. d. chir. **4**:127, 1908.

36. Mueller, Ludwig: Das corrosive Geschwür im Magen und Darmkanal (Ulcus ventriculi perforans chronicum rotundum), und dessen Behandlung, Stuttgart, Ferdinand Enke, 1860, p. 274.

37. Gundermann, W.: Production expérimentale d'ulcères gastriques et duodénaux; contribution à l'étude d'une fonction pathologique du foie, J. de chir. **12**:635, 1914.

38. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Eck Fistulas on Certain Diets, Arch. Path. **4**:492 (Sept.) 1927.

Eshker and Widal and Meslayo, the staphylococcus; Chantmesse and Widal, bacillus of dysentery; Bieulafoy, Benzancon and Griffen, pneumococcus; Saltineano, a coccobacillus and the bacillus of Pfeiffer; Favre, an organism from the blood of a patient with eclampsia, and Rodet and Zaidmann, *Bacillus coli*. The results of these studies were variable, usually with the production of certain gastric erosions.

Ingestion of Bacteria.—Subsequent investigators have adopted two definite methods: the introduction of bacteria by ingestion, or by intravenous injection. Sometimes concomitant procedures were adopted to enhance the action of the bacteria; for example, the production of an artificial anemia. Turck [39] produced both acute and chronic ulcers by feeding *Bacillus coli-communis* obtained from the feces of a patient with ulcer to a series of dogs over a long period of time; negative results were observed after the intravenous injection of the same organism. Singer [40] mixed excreta with the food and observed varying results, but never any lesions comparable to chronic ulcer. Ivy fed cultures of virulent streptococci, and at the same time produced lesions at the pylorus by pinching the mucosa. In five normal dogs the lacerations healed in from five to ten days; in five cachetic animals indurated ulcers occurred in from four to six weeks, and acid was absent in the stomach. He believed that with hypo-acidity swallowed bacteria were implanted in petechial hemorrhages or erosions, and, as a consequence, inflammation and induration of the edges, associated with a defective blood supply, delayed the regeneration of the mucous membrane. Although the general condition improved, chronicity persisted in the ulcer, due, he believed, to the diminished blood supply, the mechanical irritation by coarse foods, the tonic gastric activity and the action of acid pepsin on the devitalized tissue in the base of the ulcer. Rosenow [41] could not demonstrate the formation of ulcer after the oral administration of

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39. Turck, F. B.: Experiments in Producing Artificial Gastric Ulcer and Genuine Induced Peptic Ulcer, J. A. M. A. **46**:1753 (June 9) 1906; Further Observations on the Etiology and Pathology of Peptic Ulcer, Brit. M. J. **1**:922, 1907; Experimental Studies on Round Ulcer of the Stomach and Duodenum, J. M. Research **17**:365, 1907-1908.

40. Singer, quoted by Greggio: Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

41. Rosenow, E. C.: The Production of Ulcer of the Stomach by Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913; Pathogenesis of Spontaneous and Experimental Appendicitis, Ulcer of Stomach and Cholecystitis, J. Indiana M. A. **8**:458, 1915; The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333, 1916; Focal Infection and Elective Localization of Bacteria in Appendicitis, Ulcer of Stomach, Cholecystitis, and Pancreatitis, Surg. Gynec. Obst. **33**:19, 1921; The Etiology of Spontaneous Ulcer of the Stomach in Domestic Animals, J. Infect. Dis. **32**:384, 1923; The Specificity of the Streptococcus of Gastroduodenal Ulcer and Certain Factors Determining Its Localization, ibid. **33**:248, 1923. Rosenow, E. C., and Sanford, A. H.: The Bacteriology of Ulcer of the Stomach and Duodenum in Man, J. Infect. Dis. **17**:219, 1915.

streptococcic strains which produced lesions by intravenous injection, even after the admixture of sharp particles to the diet. Wilensky and Geist [42] isolated streptococci according to Rosenow's technic, excised a piece of gastric mucosa and injected the organism into the defect at the time of operation. The injection was repeated subsequently when it tended to heal. The characteristics of chronic induration failed to develop in any ulcer and healing was not retarded.

Kotzareff and de Morsier,[43] continuing the work of Askanazy [44] and Kotzareff, injected *Oïdium albicans* into local defects in the gastric mucosa of dogs, pigs, guinea-pigs and rabbits. They began their injections twenty-four hours after scraping the mucosa from the lesser curvature and the pylorus, and continued them daily for twenty days. The animals died with acute gastritis, or with perforated or chronic perforating ulcer, and the organism was recovered from the lesion.

Injection of Bacteria.—More definite and constant results have followed the injection of organisms into the blood stream. Steinharter [45] reported the production of gastric and duodenal ulcers following the intravenous injection of a staphylococcus isolated from an acutely inflamed appendix; the ulcers varied in size from 1 to 7 mm. and were cleanly punched out and circumscribed. Previously, he reported [46] the production of acute superficial ulcer following the injection of *Bacillus coli-communis* into the vein of an ear of a rabbit; also after the injection of *Staphylococcus pyogenes* into the wall of the stomach with the simultaneous administration of weak acetic acid by mouth. Hoffman [47] claimed that he isolated a comma-shaped bacillus from the gastric contents in a case of ulcer which, on intraperitoneal injection into a guinea-pig, produced lesions of the stomach and duodenum with duodenitis. The organism was recovered and cultivated, and the lesion was reproduced on second animal passage, thus conforming to Koch's laws.

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42. Wilensky, A. O., and Geist, S. H.: Experimental Studies in the Production of Chronic Gastric Ulcer, J. A. M. A. **66**:1382 (April 29) 1916.

43. Kotzareff, A., and de Morsier, J.: Étiologie et pathogénie de l'ulcère chronique de l'estomac. Travail expérimental, Zentralbl. f. Chir. **52**:1404, 1925.

44. Askanazy, M.: Ueber Bau und Entstehung des chronischen Magengeschwürs, sowie Scorpilzbefunde in ihm, Virchows Arch. f. path. Anat. **234**:111, 1921.

45. Steinharter, E. C.: Gastric Ulcer Experimentally Produced by Means of the Staphylococcus Organism: A Preliminary Note, Boston M. & S. J. **174**:678, 1916.

46. Steinharter, E. C.: A Preliminary Note on the Experimental Production of Gastric Ulcers by the Intravenous Injection of Clumped Colon Bacilli, Boston M. & S. J. **169**:81, 1913; Gastric Ulcer Produced by the Intravenous Injection of Staphylococcus Pyogenes, ibid. **176**:461, 1917.

47. Hoffman, A.: Experimental Gastric and Duodenal Inflammation and Ulcer, Produced with a Specific Organism Fulfilling Koch's Postulates, Am. J. M. Sc. **170**:212, 1925.

Hoffman believed it to be a specific organism with selective affinity for the stomach and duodenum. Kobayashi [48] tied the cecum of a dog so that the peritoneum would become inflamed, and thus produced ulcers. Saitta [49] associated vagotomy or trauma with the injection of bacteria, but with varying results. Having observed that the injection of diphtheria toxin had produced erosions in the stomach, Rosenau and Anderson [50] injected washed diphtheria bacilli into guinea-pigs, with resulting congestion, hemorrhage or ulceration near the pylorus. Hardt [51] was able to produce lesions following the injection of *Bacillus coli* in only four of eighteen cases (22 per cent), but following the injection of streptococci the ulcer incidence was 57 per cent; seven of these occurred in eight dogs with a Pavlov pouch, many in the pouch itself. This he claimed eliminated the mechanical and acid factors in the production of ulcer.

Specific Streptococci.—Recent studies have been directed toward determining the relationship of streptococci to the formation of ulcer. Ivy injected streptococci into branches of the gastro-epiploic vessels, causing dense fibrinous and fibrous perigastritis, but not ulceration. He concluded that a markedly virulent or specific bacterium is necessary to produce gastric ulceration. Celler and Thalhimer [52] recovered a hemolytic streptococcus from gastric ulcers, which, when injected intravenously into rabbits, caused gastric lesions in 13.3 per cent; when this substance was injected into a branch of the gastric artery, lesions were observed in 75 per cent of the cases. Saccharomyces and a gram-negative bacillus were also isolated with the streptococcus. From seventeen cases of chronic gastritis or duodenal ulcer, Haden and Bohan [53] isolated a streptococcus which on injection showed gastric and duodenal lesions in 53 per cent of forty-five rabbits. As controls, streptococci from patients not having ulcers were injected into 535 rabbits, and gastric and duodenal lesions resulted in only 7 per cent.

The outstanding contribution on the relationship of streptococci to the formation of ulcer has been Rosenow's work [41] relating to the elec-

48. Kobayashi, quoted by Greggio: Arch. de méd. expér. et d'anat. path. **27:** 533, 1916-1917.

49. Saitta, S.: Contributo alla pathogenesi dell' ulcera gastrica, Gazz. d. osp. **21:**599, 1900.

50. Rosenau, M. J., and Anderson, J. F.: A Stomach Lesion in Guinea-Pigs Caused by Diphtheria Toxin and Its Bearing upon Experimental Gastric Ulcer, J. Infect. Dis. **4:**1, 1907.

51. Hardt, L. L.: Contributions to the Physiology of the Stomach: XXXIII. The Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcers, Am. J. Physiol. **40:**314, 1916.

52. Celler, H. L., and Thalhimer, William: Bacteriological and Experimental Studies on Gastric Ulcer, J. Exper. Med. **23:**791, 1916.

53. Haden, R. L., and Bohan, P. T.: Focal Infection in Peptic Ulcer, J. A. M. A. **84:**409 (Feb. 7) 1925.

tive localization of streptococci. He postulated that to prove the relationship of a specific strain of streptococcus to ulcer, it is necessary to demonstrate the organism in the ulcer, and to prove by injection that it can reproduce the lesion. He reported histologic studies of a series of ulcers and of their regional lymph nodes, in which streptococci were demonstrated, always most numerous where there was leukocytic infiltration of the subperitoneum. Using dextrose-brain broth, which supplied a gradient of oxygen tension, he cultivated the organisms isolated from ulcers, and from foci of infection in patients with ulcer. His theory is that by sojourn in the body in a focus, these streptococci acquire a specificity by virtue of which they are capable of elective localization in special tissues. To prove this he injected these specific strains of streptococci into rabbits. Hemorrhagic erosions and ulcerations resulted in 61 per cent of rabbits injected with ulcer strains, and in 28 per cent of those injected with strains from foci of the patients with ulcer. The incidence of ulcer was materially reduced by preliminary treatment with vaccine. Careful studies of joints, heart, nerves and other organs showed associated lesions in very low percentages. For a control study he injected nonspecific strains of streptococci into rabbits; gastric hemorrhage resulted in only 20 per cent of cases, and ulcer in only 9 per cent. The specific organisms lodge primarily in the interstitial tissue of the glands; hemorrhage, necrosis and ulceration follow.

Rosenow stated that the lesions resemble ulcers of patients, in situation and in gross and microscopic appearance, tending to become chronic and to perforate and cause fatal hemorrhage. The virulence of the specific strains is low, as death does not follow intraperitoneal injection into mice; nonspecific strains cause a mortality rate of 91 per cent. After cultivation on artificial mediums or after animal passage, the capacity for elective localization is retained only in 30 per cent of cases, and the organisms tend to shift, for example, from the stomach to the appendix or the gallbladder. Rosenow considers these organisms specific because of their apparent constant occurrence in the depths of ulcers of patients, to the exclusion of other organisms, and because they tend to localize in the stomach and duodenum of animals into which injections have been made, a property which is not exhibited by other organisms.

Haden,[54] Nickel and Hufford[55] and Nakamura[56] have done considerable work corroborating Rosenow's results. Using the technic described, Haden studied twelve cases of peptic ulcer from the stand-

54. Haden, R. L.: The Elective Localization of Bacteria in Peptic Ulcer, Arch. Int. Med. **35**:457 (April) 1925.

55. Nickel, A. C., and Hufford, A. R.: Elective Localization of Streptococci Isolated from Cases of Peptic Ulcer, Arch. Int. Med. **41**:210 (Feb.) 1928.

56. Nakamura, T.: A Study on Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, Ann. Surg. **79**:29, 1924.

point of dental infection. With cultures of streptococci obtained from diseased teeth extracted from patients with ulcer, he produced lesions of the stomach and duodenum in 53 per cent of forty-five rabbits which had received intravenous injections. Nakamura, in studying the dependence of symptoms of ulcer on foci of infection, noted that in nine patients the symptoms (including hemorrhage) were relieved by removal of the foci. In 70 per cent of sixty-six rabbits that received injections of the organisms from these foci, hemorrhagic erosions or ulcers were found near the pylorus; a low percentage of lesions was found in other organs. He emphasized the importance of foci of infection rather than of suture material in causing recurrence of ulcer at the line of anastomosis. Nickel and Hufford found a definite infective focus in all but one of eighty cases of duodenal ulcer; from these they isolated green-producing streptococci which produced lesions in the stomach and duodenum of rabbits when injected intravenously. Moody [57] studied the pathogenicity of *Streptococcus viridans* recovered from chronic alveolar abscesses in persons with rheumatism, in those with various different systemic disorders and in those perfectly well otherwise. In all the groups the percentage of localization in the stomach was high. He concluded that the lesions produced by organisms from persons without systemic disease are identical with those produced by organisms from persons with systemic disease. He admitted, however, the possibility of well persons later developing systemic disease from such foci. He stated, "There is evidence for and against the property of elective affinity of streptococci, but it cannot be determined wholly by some property inherent in the organism itself." Meisser [58] produced chronic foci in dogs by devitalizing four cuspids and injecting specific streptococci into the canals. He found hemorrhages or ulcerations or both in the stomach and duodenum of 65 per cent of the series of dogs.

Mention should be made here of the theory of inflammatory ulcer, based on the histologic studies of stomachs that have been resected for ulcer. These studies, although not experimental, have been carried out chiefly by Konjetzny,[2] Moszkowicz,[59] Orator,[60] Lehmann [61] and Puhl.[62]

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57. Moody, A. M.: Lesions in Rabbits Produced by Streptococci from Chronic Alveolar Abscesses, J. Infect. Dis. **19**:515, 1916.

58. Meisser, J. G.: Further Studies on Elective Localization of Bacteria from Infected Teeth, J. Am. Dent. A. **12**:554, 1925.

59. Moszkowicz, Ludwig: Zur Histologie des Ulcus bereiten Magens, Arch. f. klin. Chir. **122**:444, 1922.

60. Orator, V.: Ueber die funktionelle Bedeutung der Magenstrasse und die cardianahen Geschwüre, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:725, 1923.

61. Lehmann, J. C.: Neuere Anschauungen über die Pathogenese des Magenulcus und Karzinomas, München. med. Wchnschr. **1**:410, 1925.

62. Puhl, Hugo: Ueber die Bedeutung entzündlicher Prozesse für die Entstehung des Ulcus ventriculi et duodeni, Virchows Arch. f. path. Anat. **260**:1, 1926.

Because of the investigation of thousands of resected stomachs, these authors believe that in most cases of gastric or duodenal ulcer there exists gastritis or duodenitis. Puhl reported a series of cases in which the specimens were fixed immediately after removal. Abundant leukocytic infiltration, congestion and edema of the antrum, with ulcerations so numerous as to be called ulcerous gastritis, were found on histologic study. This inflammatory gastritis and duodenitis, with the accompanying superficial erosions, establish, according to this investigator, the necessary initial lesion for the subsequent development of chronic gastric ulcer. He observed gram-positive diplococci in the tissues, but since he was unable to culture them, he did not draw conclusions as to their significance.

TOXIC MANIFESTATIONS

The idea that a local injury to the gastric mucosa acts as the initial cause of ulceration has led to an extensive study of the effects of drugs and physical agents in causing ulceration of the mucosa of the stomach. These have been administered both systematically and locally. Bolton [14] reviewed the work of early investigators who sought to produce lesions by the systemic action of drugs. Overbach rubbed gray ointment into the skin for a period of three months; von Mering injected glycocholate of mercury into cats and dogs; Pillet and Cathetineau used perchloride of mercury; Filhene used arsenious acid. Greggio's review added the work of Virchow and Ebstein, who used phosphorus poisoning; Brouardel and Böhm, who injected arsenious acid subcutaneously; Majer, d'Auitolo and Coen, who caused progressive poisoning of rabbits and dogs with lead acetate; Sarkowsky and Heilborn, who injected corrosive sublimate subcutaneously into rabbits; Ebstein and Peron, who used alcohol; Aufrecht, who used cantharides, and Roy and Poncet, who used ergot and digitalis.

Rehfuss [63] studied the effect of the subcutaneous injection of policarpine. Injections into guinea-pigs caused ulcer and hemorrhagic erosions in 85 per cent of cases; the effect of the drug was aggravated by the simultaneous administration of atropine. Haden has shown that industrial poisoning, as by benzene (C_6H_6), may cause lesions in the duodenum. Friedman,[64] by repeated injections of epinephrine for a period of from one to two weeks, produced duodenal ulceration. He also noted that after injections of pilocarpine the preponderance of lesions was in the gastric mucosa. Elliott [65] caused acute gastric ulcers by

63. Rehfuss, M.: The Experimental Production of Acute Toxic Ulcer of the Stomach, Univ. Penn. M. Bull. **22**:105, 1909-1910.

64. Friedman, G. A.: The Experimental Production of Lesions, Erosions and Acute Ulcers in Rabbits, by Repeated Injections of Pilocarpin and Adrenalin, J. M. Research **38**:449, 1918.

65. Elliott, T. R.: The Experimental Formation of Acute Gastric Ulcers, Quart. J. Med. **7**:119, 1914.

injecting tetrahydro-B-naphthylamine hydrochloride subcutaneously into a guinea-pig. The lesions formed within one or two hours if the stomach was kept filled with food; they were healed and covered with epithelium in three days, the glands regenerating later. Westphal, as has been noted, administered to rabbits large cutaneous doses of pilocarpine, either alone or combined with physostigmine, with resulting ulcers and erosions. He believed that these lesions resulted from vascular spasm due to extreme vagal irritation. In 1917, Murata [66] repeated these studies with the same results, but he ascribed the local ischemia to obstruction of the supplying artery by a spasmodic contraction of the gastric musculature. In the same year, Hayashi [67] produced ulcerous changes following the subcutaneous injection of nicotine into guinea-pigs. Later, Hayashi [28] caused similar lesions in rats with muscarine; he attributed the result to the elective action of this poison on the stomach by peripheral vagal irritation. The use of morphine, physostigmine, epinephrine and atropine has been mentioned.

Submucous Injection.—The effect of toxic agents when injected directly into the gastric wall has been thoroughly investigated. Greggio in his review stated that Borszéky and Baron produced ulcers by injecting formaldehyde into the gastric mucosa; Rosenbach and Eschker used epinephrine; Serzuki, Payr and Vigliani injected alcohol and chloral; Serzuki used epinephrine, silver nitrate and formaldehyde; Licini,[68] after injecting apomorphine into the musculature of the stomach, noted hypermotility which changed acute to chronic lesions. Greggio himself produced gastritis with injections of alcohol, but could not induce ulcer to form. Turck sought to produce ulcerous changes by feeding mustard over a period of fourteen months, but with negative results. Ivy produced lesions by injecting 1 cc. of 5 per cent silver nitrate into the submucosa. Friedman and Hamburger [69] used the same procedure associated with partial pyloric stenosis; hyperacidity resulted, ulcers near the pylorus became chronic, and those in the cardia tended to heal. Acute ulcers, which Dragstedt and Vaughan [70] observed after injecting silver nitrate, persisted for from three to four months and tended to

66. Murata, quoted by Hayashi: Ztschr. f. d. ges. exper. Med. **34**:224, 1923.

67. Hayashi (footnote 28, page 227).

68. Licini, Cesare: Ueber experimentelle Erzeugung von Mageneschwüren, Beitr. z. klin. Chir. **79**:462, 1912.

69. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer: A Second Contribution to the Experimental Pathology of the Stomach, J. A. M. A. **63**:380 (Aug. 1) 1914.

70. Dragstedt, L. R., and Vaughan, A. M.: Gastric Ulcer Studies. The Resistance of Various Tissue to Gastric Digestion, Arch. Surg. **8**:791 (May) 1924. Dragstedt, L. R.: Contributions to the Physiology of the Stomach: XXXVIII. Gastric Juice in Duodenal and Gastric Ulcers, J. A. M. A. **68**:330 (March 17) 1917.

become chronic when loops of nonabsorbable suture material were embedded in the gastric walls at the points of injury. Similar ulcers were observed by Hughson [71] to remain active twice as long when associated with delayed emptying of the stomach.

Biologic Toxins.—Of greater interest are those biologic products which exert a toxic action on the gastric mucosa. Ponfick [72] observed clinical lesions of the stomach and duodenum, following superficial burns, in as short a time as eighteen hours, with associated congestion of the mucous membrane and enlarged lymphoid follicles. Silbermann,[34] Vassale and Sacchi [73] and Parrascandola caused ulcers in animals following large cutaneous burns, or by injecting the extracts of burned tissues. Greggio quoted Stoknis, Long, Sokoloff and Castel as having caused lesions by glazing the surface of the skin.

Bolton [14] produced what he called a gastrotoxic serum (and an analogous hepatotoxin and enterotoxin) by injecting a suspension of gastric mucosa from a guinea-pig into the peritoneal cavity of a rabbit. After antibodies to this foreign protein had developed sufficient to establish the rabbit's immunity to it, an injection of this immune serum into the peritoneal cavity of a guinea-pig caused death, associated with lesions of the stomach. Injection of this toxin directly into the gastric mucosa also caused ulceration. Bolton found that although ordinarily hydrochloric acid does not exercise any effect on the gastric mucous membrane in concentrations below 0.7 per cent, yet any concentration from 0.25 to 0.7 per cent caused an increase in the size of the lesion produced by injecting gastrotoxic serum, and 0.5 per cent acetic acid (usually innocuous below 2 per cent) increased a lesion produced by the injection of gastrotoxin. Miyagawa, Murai and Terada,[74] adopting the same method, produced an homologous toxic serum. They immunized one rabbit to the gastric mucosa of another rabbit, and injected the serum of this immune rabbit locally into the gastric mucosa of a third rabbit. The interpretation of the production of these ulcers was that the reabsorption of toxic substances from the necrosed tissue of an ulcer leads to the production in the organism of a cytotoxin which prolongs ulcer and leads to chronicity. Hepatotoxin and enterotoxin, produced similarly

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71. Hughson, W.: Relation of the Pylorus to Duration of Experimental Gastric Ulcer, Arch. Surg. **15**:66 (July) 1927.

72. Ponfick, quoted by Bolton: Ulcer of the Stomach, London, Edward Arnold, 1913.

73. Vassale, G., and Sacchi, E.: Sulla tossicitá dei tessuti scottati, Riforma med. **9**:544, 1893.

74. Miyagawa, Yoneji; Murai, Hatsu, and Terada, Masachika: An Experimental Study of the Cells of the Mucous Membrane of the Digestive Tract as Toxin or Irritant, and Its Relation to the Formation of Peptic Ulcer, Japan M. World **3**:123, 1923.

from hepatic and intestinal tissues, were not so certain in their action as gastrotoxin, nor were they specific for a single species.

Latzel [75] sterilized the gastric juice of a guinea-pig, and by subcutaneous injections into other animals caused anaphylaxis and ulceration of the stomach. Jona [76] caused similar changes and inhibited pancreatic secretion by subcutaneous doses of extracts of decomposing animal tissues. Greggio, quoting the older workers who used biologic toxins, said that Loepez caused ulcerous changes by injecting a watery maceration of the mucosa or gastric juice of swine; Gundermann [37] caused it with extract of liver; Stick, with ptomaines, and Favre, with the blood of a uremic person. In corroboration of the work of Enriquez and Hallion (quoted by Bolton), Rosenau and Anderson [50] found that diphtheria toxin, when injected into guinea-pigs, caused hemorrhage and necrotic patches in the gastric mucosa. They found lesions in 66 per cent of guinea-pigs used in the production of antitoxin. If, however, the toxin was neutralized by antitoxin, a lesion did not appear. Necropsy revealed congestion, hemorrhage or ulceration at the pyloric extremity, associated with congested suprarenal glands and pleural effusion. Such results were not obtained with tetanus toxin or chemical poisons.

As an extension of his work on the elective localization of streptococci, Rosenow showed that the dead bacteria, or a filtrate of the living culture, possessed the same local affinity as the living organism, causing lesions in the stomach and duodenum. Ivy and Shapiro [77] injected foreign protein (albumin of egg, beef and cat protein) into the skin of a rabbit until a superficial ulcer formed from local anaphylaxis; this specific protein when later injected into the gastric mucosa caused ulcer to form.

Miscellaneous Methods.—Decker [78] produced erosions and ulcers by feeding dogs with gruel heated to 50 C. He attributed this not to the scalding but to the congestion of the mucous membrane and the hemor-

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75. Latzel, R.: Recherches expérimentale sur l'étiologie de l'ulcère de l'estomac et conséquences théoriques sur la pathogénie de l'ulcère de l'estomac et du duodénum, J. de chir. **11**:788, 1913.

76. Jona, J. L.: An Experimental Study of Duodenal Ulcer, M. J. Australia **1**:165, 1918; A Further Contribution to the Experimental Study of Duodenal Ulcer, ibid. **1**:316, 1919; Experimental Study of Duodenal Ulcer, Physiol. Abstr. **4**:412, 1919.

77. Ivy, A. C., and Shapiro, P. F.: Studies on Gastric Ulcer: III. The Experimental Production of Gastric Ulcer by Local Allergy; Preliminary Report, J. A. M. A. **85**:1131 (Oct. 10) 1925. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer: IV. Experimental Production of Gastric Ulcer by Local Anaphylaxis, Arch. Int. Med. **38**:237 (Aug.) 1926.

78. Decker, J.: Experimentelle Beitrag zur Aëtiologie der Magengeschwüre, Berl. klin. Wchnschr. **24**:369, 1887.

rhagic erosions from increased peristalsis. Katzenstein [79] introduced small, hot, porcelain tubes into the stomach to burn the mucosa; this was followed by injection of phosphoric acid to destroy antipepsin and allow digestion. Ribbert [80] froze an area, 2 cm. in diameter, of the wall of the stomach with ethyl chloride and methethyl for twelve minutes. The following day a defect appeared in the gastric mucosa, which developed subsequently into an ulcer. Wolfer [81] opened the anterior wall of the stomach, delivered the posterior wall and sutured a lead plate with a small opening to the mucosa. Through this small opening he exposed the mucosa to the roentgen rays and produced a round or oval ulcer with indurated raised margins. One of these ulcers persisted for 585 days. In a later study he noted that if such ulcers were produced close to the pylorus there was a definite delay in the emptying time of the stomach, but if farther away than 5 cm. there was no delay.

Rassers [82] eliminated all chlorides from the diet of a series of dogs, and administered twelve, eighteen, twenty and twenty-four doses of strong acid pepsin solution over a period of from one to three days. He observed hemorrhagic erosions and small ulcerations in the pyloric antrum and duodenum, which he attributed to the failure of the cells to produce a protective hydroxide against the acid pepsin which was administered.

Kirch and Stahnke,[83] observing that in chronic ulcers the muscularis propia is always absent, produced mucosal defects in the stomachs of a series of dogs, and cut away the underlying muscle. From their results they concluded that destruction of the muscle delays healing and is an important factor in the chronicity of lesions, although it does not prevent healing. Morton,[32] however, noted that healing took place with almost as great ease and rapidity when the muscularis was excised as when the mucosa alone was excised.

Baggio [84] folded in the anterior wall of the stomach and observed lesions ranging from simple erosions to typical advanced gastric ulcers

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79. Katzenstein, M.: Der Schutz des Magens gegan die Silbstverdauung nebst einem Vorschlag zur Behandlung des Ulcus ventriculi, Berl. klin. Wchnschr. **45**: 1749, 1908. Quoted by Smith: J. M. Research **30**:147, 1914.

80. Ribbert, H.: Experimentelle Magengeschwüre, Frankfurt. Ztschr. f. Path. **16**:343, 1915.

81. Wolfer, J. A.: Chronic Ulcer of the Stomach: Its Experimental Production and Effect on Gastric Secretion and Motility, Ann. Surg. **84**:89, 1926; Chronic Experimental Ulcer of the Stomach: Its Clinical Significance, J. A. M. A. **87**:725 (Sept. 4) 1926.

82. Rassers, J. R. F.: The Pathogenesis of Chronic Gastro-Intestinal Ulcer and Some Remarks on the Question of a Rational Therapy, Surg. Gynec. Obst. **45**:345, 1927.

83. Kirch, E., and Stahnke, E.: Delayed Healing of Chronic Gastric Ulcer from Destruction of Muscle, Frankfurt. Ztschr. f. Path. **33**:269, 1925-1926.

84. Baggio, G.: Experimental Gastric Ulcer from Obstruction to the Emptying of the Stomach, Surg. Gynec. Obst. **44**:490, 1927.

on both the introflexion and the posterior wall opposite the introflexion. He attributed these lesions to the traumatic action of the ingesta and the obstruction caused by the introflexion. Slocumb [85] noted inflammatory changes and multiple ulcers in the duodenum of dogs in which he established partial obstruction of the duodenum by surgical measures.

Ivy noted five ulcers in forty dogs subjected to pylorectomy and gastroduodenostomy. Borszéky [86] narrowed the pylorus and performed gastro-enterostomy on twelve dogs; he fed them 30 cc. of dilute hydrochloric acid daily. Jejunal ulcers formed only in one of twelve dogs. Dott and Lim [87] claimed that they observed jejunal ulcers in 90 per cent of the dogs on which they performed pyloric exclusion and gastrojejunostomy. Montgomery [88] found chronic jejunal ulcers in four of sixty dogs on which gastro-enterostomy had been performed. Exalto [89] performed gastro-enterostomy after excluding the pylorus; he then drained the duodenal alkalis of the proximal loop into the cecum. He observed jejunal ulcer, often multiple, in six of ten dogs operated on in this manner.

TROPHIC AND GLANDULAR ULCERS

A different conception of ulcer formation has directed the great volume of work accomplished by the Italian school. They interpret the lesion as of a neurotrophic order, dependent on a defect in the nerve supply to the stomach. Their researches have dealt chiefly with the influence of the vagi, although they have also investigated the central nervous system and splanchnic nerves.

Central Nervous System.—Ebstein [90] and Brown-Séquard,[91] in the earliest studies on the central nervous system, obtained partial softening, erosion and formation of ulcer in the stomach following circumscribed destruction of the anterior corpora quadrigemina, and after burns of the

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85. Slocumb, L. H.: Experimental Gastroduodenal Ulcer Produced by Partial Obstruction of Duodenum, J. Missouri M. A. **24**:351, 1927.

86. Borszéky, Karl: Die chirurgische Behandlung des peptischen Magen und Duodenalgeschwürs und seiner Komplikationen und die damit erreichten Endresultate, Beitr. z. klin. Chir. **57**:56, 1908.

87. Dott, N. M., and Lim, R. K. S.: Experimental Jejunal Ulcer, Quart. J. Exper. Physiol., Suppl., 1923, p. 109.

88. Montgomery, A. H.: Gastrojejunal Ulcer: An Experimental Study, Arch. Surg. **6**:136 (Jan.) 1923.

89. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:13, 1911.

90. Ebstein, Wilhelm: Experimentelle Untersuchungen über das Zustandekommen von Blutextravasaten in der Magenschleimhaut, Arch. f. exper. Path. u. Pharmakol. **2**:183, 1874.

91. Brown-Séquard, quoted by Greggio: Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917. Quoted by Zironi: Arch. f. klin. Chir. **91**:662, 1910.

cerebral surfaces. Schiff [92] observed hemorrhagic infiltrations and ulcerations following intersection of the thalamus and cerebral peduncles. Greggio noted mucosal and submucous hemorrhages near the pylorus, associated with diffuse gastritis, in half of fifty cases subjected to unilateral and median compression of the cervical cord. He and Bolton cited the production of ulcer by Albertoni, who cut off the cerebral hemisphere; Ewald and Koch, who severed the cervical cord and administered 0.5 per cent hydrochloric acid daily; Schupfer, following bilateral lesions of the anterior and posterior roots of the fifth and eighth dorsal segments, and Quincke and Dättwyler,[93] who associated lesions of the cord with anemia.

Splanchnic Nerves.—While Durante [94] was studying the relationship of the splanchnic or sympathetic nerves to ulcerous changes, he repeated the work of dalla Vedova.[95] He resected the splanchnic nerves by a lumbar approach, and found that section of the median splanchnic nerve produced circumscribed hemorrhagic or nonhemorrhagic necrosis of the gastric mucosa. The hemorrhagic areas began in the blood vessels of the muscularis mucosae, destroying only the mucosa, and there was evidence of slow regeneration. The nonhemorrhagic type involved the mucosa and submucosa, but did not show signs of regeneration. He considered that the latter type might have resulted from arterial spasm due to the action of epinephrine, because he observed simultaneous intense congestion with signs of hemorrhage in the suprarenal gland on the side of resection. Section of the minor splanchnic nerve caused only occasional lesions, and of the major splanchnic nerve only transient congestion. Since both acute and chronic ulcers occurred, he did not consider that time was an important factor in their formation. Koennecke [96] observed that excision of the pylorus followed by a Billroth I or a Billroth II operation caused jejunal ulcer in one of five dogs, but bilateral division of the splanchnic nerves following the same procedure caused typical callous deeply penetrating ulcers in all dogs. He attributed this result to removal of an inhibition to secretion.

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92. Schiff, J. M.: Leçons sur la physiologie de la digestion, Florence, H. Loescher, 1867, vol. 2, p. 557.

93. Quincke and Dättwyler, quoted by Bolton: Ulcer of the Stomach, London, Edward Arnold, 1913.

94. Durante, Luigi: The Trophic Element in the Origin of Gastric Ulcer, Surg. Gynec. Obst. **22**:399, 1916.

95. Dalla Vedova, Riccardo: Richerche sperimentali sulla patogenesi dell' ulcera gastrica, Policlinico **6**:1153 (Suppl.) 1900.

96. Koennecke, W.: Experimentelle Untersuchungen über die Bedeutung des Pylorusmagens für die Ulcusgenese, Arch. f. klin. Chir. **120**:537, 1922; ibid., Zentralbl. f. Chir. **50**:276, 1923; Ulcusgenese und Gastroenterostomie, ibid. **53**: 1866, 1926.

Celiac Plexus.—Gundelfinger,[97] after extirpation of the celiac ganglion (by which the action of the sympathetic was removed from the stomach and duodenum, leaving only vagal influence), succeeded in producing gastric lesions. Latzel [75] reported negative results after extirpation of the celiac plexus. Greggio, in his comprehensive review, reported ulceration of the gastric mucosa and hyperemia in the liver following extirpation of the celiac plexus by Pincus and Samuel, Löwin, Boer and Popielski; others have failed to produce them by this procedure in dogs and rabbits, for example, Adrian, Budge, Lustig, Lamansky and Peiper. Lesions of the plexus were found to produce ulcers and mucous hemorrhages by dalla Vedova,[95] Kawamura,[98] and Lilla and Gibelli.[35] On the other hand, Donati,[99] Kobayashi,[48] Lorenzi [100] and Schmincke [100] observed negative results or only small hemorrhages by irritation of the plexus. Brancati [100] found that ablation of the paravertebral lumbar sympathetic in a dog caused capillary dilatation, necrosis of the mucosa and ulcers at the pyloric region of the stomach and in the adjacent part of the duodenum.

The Vagi.—There has been a much more extensive investigation of the relationship of vagal influence to gastroduodenal lesions. Resection of both vagi in the neck of rabbits was found by Lorenzi to produce hemorrhage in the gastric mucosa fairly frequently. Saitta,[49] after bilateral vagotomy, observed multiple ulcers when he administered 3 per cent hydrochloric acid by mouth. Finzi [101] noted that extirpation of one vagus yielded inconstant results, but that bilateral vagotomy produced, with greater regularity, circulatory disturbances, edema, ecchymosis, necrotic processes and atrophic ulceration. Keppich [102] reported the formation of ulcer in five cases following resection of the vagus. According to Greggio, negative results following vagotomy in the neck of a rabbit are reported by Donati, Kobayashi, Körte and Martini; however, Midulla found that sectioning the vagus in the neck of frogs and

97. Gundelfinger, Ernst: Klinische und experimentelle Untersuchungen über den Einfluss des Nervensystems bei der Entstehung des runden Magengeschwürs, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **30**:189, 1918.

98. Kawamura, K.: Zur Frage der Verdauung lebenden Gewebes im Magen, zugleich ein Beitrag zur Pathogenese des runden Magengeschwüres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:379, 1913.

99. Donati, M.: Experimentelle Versuche das Magengeschwür vermittels Verletzungen der Magennerven hervorzurufen, Zentralbl. f. Chir. **31**:346, 1904.

100. Lorenzi; Schmincke, and Brancati, quoted by Greggio: Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

101. Finzi, Otello: Ueber Veränderungen der Magenschleimhaut bei Tieren nach Nebennierenexstirpation und über experimentell erzeugte Magengeschwüre, Virchows Arch. f. path. Anat. **214**:413, 1913.

102. Keppich, Josepf: Künstliche Erzeugung von chronischen Magengeschwüren mittels Eingriffe am Magenvagus, Wien. klin. Wchnschr. **34**:118, 1921.

toads caused gastric dilatation, spasm of the pylorus, hypersecretion of the gastric juice, and ulcers which showed a tendency to become chronic and perforate.

The thoracic approach to the vagus has been utilized by others. Zironi,[33] after cutting the vagi around the esophagus of rabbits, observed ulceration in fifty-nine of 100 experiments. Antonini [103] observed ulcers in only seven of 100 animals after the same procedure; the day following operation there was gastric dilatation and congestion, with the development of lesions possessing the same gross and microscopic appearances as peptic ulcer in man. Cicatrization was not observed. In lesions observed after twenty, twenty-five and fifty days, there was no evidence of healing. Greggio frequently produced hemorrhagic infiltration of the mucosa after bilateral vagotomy, but in only one case did he find a chronic ulcer. This ulcer was 2 cm. in diameter and was situated on the greater curvature. He quoted negative results following this procedure by Krehl, Futsch, Kawamura, Rubaschoff, Muziolli and Fiori, and inconstant results by Samuelson and Contejan.

Thorough studies have been carried out following resection of the vagi in the abdomen. Zironi claimed to have produced gastric ulcer in sixty-four of 100 rabbits following subdiaphragmatic vagotomy. Lorenzi duplicated these observations. Van Yzeren cut both vagi subdiaphragmatically in twenty rabbits; in ten of them he found chronic single ulcers, usually near the pylorus; the earliest was observed in five days and the oldest in 289 days. Ophuls,[104] repeating these studies with the same results, concluded that the lesions were neurotrophic, and that trophic influences are necessary to preserve the normal resistance of the mucous membrane to the digestive action of the gastric juice. Latzel [75] noted hemorrhagic erosions and ulcerations in ten dogs following subdiaphragmatic vagotomy. Zironi, after similar resection in guinea-pigs, found lesions varying from 0.3 to 1 cm. in diameter in 63 per cent of his studies. Donati [99] reported negative results after a thorough study by this method. Greggio quoted Gunsburg and Lundi and Kobayashi and Marchetti as having caused diffuse changes in the mucosa or actual ulcers by this procedure; Saitta, Gibelli, Finachiaro, Lilla and Vigliani reported negative results.

Stimulation of the vagus has given contradictory results. Stahnke,[105] in studying the effect of long continued vagal stimulation on gastric

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103. Antonini, Leopoldina: La resezione intratoracica laterale del vago nei suoi rapporti con la patogenesi dell' ulcera rotonda dello stomaco, Riforma med. **1**:88, 1914.

104. Ophuls, W.: Gastric Ulcers in Rabbits Following Resection of the Pneumogastric Nerves Below the Diaphragm, J. Exper. Med. **8**:181, 1906.

105. Stahnke, Ernst: Experimentelle Untersuchungen zur Frage der neurogenen Entstehung des Ulcus ventriculi zugleich ein Beitrag zur pathologischen Physiologie der Mageninnervation, Arch. f. klin. Chir. **132**:1, 1924.

motility and secretion, faradized the vagi for forty minutes. At necropsy gastritis of the mucosa was found in some dogs, and superficial defects in the mucosa were found in others. He considered the ulceration to be a result of increased secretion and chronic gastritis. Keppich,[102] by stimulating the vagi of rabbits with electrodes, produced chronic gastric ulcer in ten of eleven surviving animals. Westphal [25] believed that extreme vagal irritation explained the ulcers following the injection of pilocarpine. Hayashi interpreted similarly the lesions produced by muscarine. Gundelfinger was unable to produce ulcers by vagal irritation. Greggio cited Talma and Lichenbeld as having produced lesions by excitation of the vagus; Lorenzi and dalla Vedova, after burns and alcoholic injections into the vagus, caused hemorrhage and ulceration of the stomach. Negative results were reported by Korte and Donati.

The combination of these various procedures has given rather inconstant results. Donati recorded negative results after abdominal section of the vagi and extirpation of the celiac plexus. According to Greggio, Samuelson noted negative results following the same procedure, with the administration of hydrochloric acid in addition; on the contrary, Lilla found that this surgical procedure alone yielded small punctate hemorrhages of the mucosa. Induced anemia seems to augment these neurotrophic lesions. Zironi increased the incidence of ulcer following thoracic and subdiaphragmatic resection of the vagi from 59 to 80 per cent by inducing artificial anemia; he also claimed to observe an acute ulcer assume chronicity coincident with induced anemia. Greggio caused lesions by vagotomy and the simultaneous administration of alcohol. Vagotomy associated with ligation of the pyloric artery and excision of the mucosa at a corresponding area produced complete healing and cicatrization in three months. Abdominal vagotomy with partial pyloric stenosis gave negative results. By injection of neurine which acts by paralyzing the motor, sensory and secretory terminal fibers to the stomach, Bedarida [106] produced trophic ulcers in the stomach of rabbits. Finally, Auer [107] induced ulcerous changes by removing all the nerve supply of the stomach, which resulted in paralysis, diminished movements and suppressed reflexes. Histologic studies of the terminal nerve endings in ulcers have been made by Perman, Nikolaysen and Askanazy, as reviewed by Okkels.[108] The latter found internal inflammatory

106. Bedarida, N. V.: Produzione sperimentale di ulcera gastrica, Arch. ital. de chir. **9**:109, 1924.

107. Auer, quoted by Greggio: Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

108. Okkels, H.: Pathologic Changes in the Nerves of the Stomach Wall in Cases of Chronic Gastric Ulcer, Am. J. Path. **3**:75, 1927.

changes of the perineural sheath of nerve branches in the myogastric plexus, nerves embedded in connective tissue and proliferative central cicatrix neuromas. He considered these changes as secondary and nonspecific, but believed that they may contribute to the chronicity of ulcers.

The theoretic interpretation of these results is of interest. Greggio concluded that vagotomy alters gastric motility, delays emptying of the chyme into the intestine, causing dilatation of the stomach and possibly interference with the mechanism of the pylorus. Von Bergmann [109] believed that hypertonicity of the vagus produces gastric spasm which puckers the gastric mucosa, strangles it and produces local ischemia and necrosis; this area is digested by the gastric juice and is eroded at its edges, and ulcer develops. Durante [94] conceived of central psychic stimuli changing the normal vasomotor tonus which might result in rupture of small arterial walls in the stomach, or toxic stimuli which might irritate the peripheral sympathetic system (the trophic nerve controlling the vasomotor nerves of the stomach) and lead to the formation of ulcer.

Glandular Influence.—The effect of glandular activity on the formation of ulcer may be viewed as associated with some type of nervous mechanism. Durante, it will be recalled, noted that ulcers following median splanchnic resections were associated with lesions of the suprarenal glands, and concluded that the effect might have been produced by suprarenal activity.

The studies of numerous investigators have indicated a possible relationship between the glands of internal secretion and the ulcerative lesions of the stomach. There are reported in the literature five cases of ulcer of the duodenum and stomach in man associated with thickening of the suprarenal capsule, hypertrophy, fatty degeneration, congestion and multiple hemorrhages into the glands. Latzel [75] reported the occurrence of ulcers in three animals following destruction of the suprarenal capsule. Greggio quoted Gibelli, Onde and Cioffi as having produced ulcer by induced suprarenal insufficiency. Mann [110] observed acute ulcerations in 90 per cent of animals following the removal of both glands, but none associated with simple removal of the capsules. Hemorrhagic areas were found in the stomach in one animal which died in twenty-four hours; definite ulcers were found in another in twenty-two hours. If the ulcers were situated in the fundus (the pylorus being normal) usually the mucosa alone was involved; if they were in the prepyloric division they penetrated the muscularis mucosae. The duo-

109. Von Bergmann, G.: Das spasmogene Ulcus pepticum, München. med. Wchnschr. **60**:169, 1913.

110. Mann, F. C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, J. Exper. Med. **23**:203, 1916.

denum was generally injected. The suggested dependence of these lesions on bile and trypsin was ruled out by their continued appearance after the establishment of a biliary and a pancreatic fistula. The acid appeared to be a factor as ulcers did not develop when sodium bicarbonate was fed to dogs on whom suprarenalectomy had been performed. Elliott [111] noted acute gastric ulcers following the removal of suprarenal glands in cats, and cited it as proof of the full digestive power of the gastric juice. Finzi [101] observed edema, congestion, hemorrhage, necrosis and ulceration with an effort to heal following suprarenal suppression. Friedman [112] found lesions in the pyloric portion of the stomach to be most frequently associated with removal of the left suprarenal gland, and in the rest of the stomach associated with removal of the right suprarenal gland.

Friedman, while studying the interrelationship with other glands, also noted that removal of one suprarenal gland and one thyroid gland did not have any effect on the integrity of the gastric mucosa, but that intravenous thyroid medication associated with this procedure caused small ulcerations. Finzi also observed that the simultaneous removal of one thyroid gland and one suprarenal gland failed to cause ulcerous changes; he assumed that suprarenal insufficiency can manifest its action on the stomach only with an intact thyroid gland, and that the correlation of internal secretions may have a bearing on the formation of ulcer. Hardt [51] studied the relationship of the feeding of thyroid gland to acidity and found that with increasing thyroid administration there was a decrease in acidity and gastric secretion, while with its interruption there was a return to the normal status. Hayashi, by imitating the so-called mixed stigmatized constitution with the administration of thyroid gland, was able to produce spasmogenic ulcerous changes. Greggio reported ulcers following thyroidectomy as having been produced by Boccardi, Grofreddi, Falcone and d'Amore. He reported ulcers following exclusion of the liver by Mueller, Kollicher, Bidder and Schmidt, Beati and others. They have been observed by Bollman and Mann [38] following insufficiency of hepatic function induced by partial hepatectomy.

DIGESTIVE JUICES

Thus far, four principal fields of experimentation, vascular, bacterial, toxic and neurologic, have been reviewed. In evaluating the results obtained, one is justified in concluding that the occurrence of ulcer has

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111. Elliott, T. R.: Some Results of Excision of the Adrenal Glands, J. Physiol. **49**:38, 1914-1915.

112. Friedman, G. A.: The Influence of Removal of the Adrenals and One-Sided Thyroidectomy upon the Gastric and Duodenal Mucosa: The Experimental Production of Lesions, Erosions and Acute Ulcer, J. M. Research **32**:287, 1915.

been variable. One investigator has observed results contradictory to those of another; true chronic indurated ulcers have been reported rarely. These studies, however, have answered a part of the problem; they have indicated a variety of means by which an initial acute lesion may be established. Probably only a few investigations (with the exception of Rosenow's work on the elective localization of bacteria) can be interpreted as of direct clinical significance. On the basis of these studies one is still confronted with the problem so aptly stated by Cohnheim in 1880: "The real difficulty in understanding simple ulcer of the stomach is not so much its mode of origin, as the circumstance that it usually so obstinately refuses to heal." He continued, referring to ulcers of embolic origin: "There must be in addition an unknown something which prevents the healing of ulcer. But whether, as has more than once been suggested, this something consists in an abnormal acidity of the gastric juice, we have as yet no positive investigation to show." Mann and his co-workers [113] have probably supplied this desideratum. By "positive investigations" considerable evidence now indicates that the "unknown something" consists in the action of mechanical factors and the disturbance of the factors of acid and alkali at the pylorus. The mechanical factors and disturbance of the optimal chemical conditions for each side of the pylorus, which result from the surgical procedures employed in these studies, are probably the sole etiologic factors in causing the experimental ulcers, and possibly form the basis for the chronicity of clinical ulcers, determining their inability to heal.

Chemical Methods.—The importance of the digestive juices in relation to ulcer has long been suspected, and many investigations have been directed toward evaluating their influence. Saitta [49] administered 3 per cent hydrochloric acid by mouth following vagotomy and found multiple ulcers, whereas without the giving of acid he observed only hemorrhagic erosions. Friedman found that ulcers in the pyloric region, caused by the submucous injection of silver nitrate, became chronic when associated with hyperacidity produced by pyloric stenosis. Litthauer [16] produced ulcer by administering 200 Gm. of hydrochloric acid to a dog, after ligation of gastric vessels and excision of a corresponding piece of mucosa. He also produced ulcers by feeding acid after having caused

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113. Mann, F. C.: The Effect on the Jejunal Mucosa of Exposure to the Gastric Juice, J. M. Research **35**:289, 1917; A Case of Spontaneous, Acute and Subacute Peptic Ulcers and Carcinoma of the Thyroid in a Dog, J. Lab & Clin. Med. **6**:213, 1920-1921; Production and Healing of Peptic Ulcer: An Experimental Study, Minnesota Med. **8**:638, 1925; The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, S. Clin. N. Amer. **5**:753, 1925. Mann, F. C., and Kawamura, Kyoichi: An Experimental Study of the Effects of Duodectomy, J. A. M. A. **73**:878 (Sept. 20) 1919; Duodenectomy: An Experimental Study, Ann. Surg. **75**:208, 1923.

anemia by injection of pyrogallic acid. Gibelli [35] failed to produce ulcers by simply administering acid by mouth. Bolton,[114] as was noted under toxic manifestations, found that hydrochloric acid did not have any effect on the gastric mucosa under a concentration of 0.7 per cent, but that after a local lesion had been produced by the injection of gastrotoxin, concentrations as low as 0.25 per cent caused an increase in the size of the lesion. Acetic acid below a concentration of 2 per cent is innocuous, yet with the lesion once established by gastrotoxin a 0.5 per cent solution increased its size. Hydrochloric acid, the only digestive juice capable of attacking connective tissue, caused necrosis of granulation tissue in the base of the ulcer, and delayed healing of the ulcer. Bolton also delayed healing of ulcers in the rabbit by artificial hyperacidity, but he discounted the acid factor because he found that ulcers did not heal any slower with a high Pavlov pouch and acid stasis than with a low pouch and free drainage. Butsch [115] clamed that acidity has some bearing on the formation of ulcer because of a higher occurrence in the Roux Y-anastomosis, in which the alkaline neutralizing factor is diminished. He also called attention to the fact that ulcer is rarely seen after anastomosis for carcinoma of the stomach, associated with diminished, or the absence of, acidity. Durante claimed that an excess of acid caused irritation and gastritis, epithelial desquamation, enlargement of the follicles and ultimately rupture and ulceration.

Smith [116] studied the relationship of bile to ulceration of the gastric mucosa. He applied a mixture of bile and acid to the mucosa of the stomach, without effect. An interrupted application, however, first of bile alone, then immediately afterward of 0.5 per cent hydrochloric acid, caused a greenish-yellow pedicle and a precipitate from the mucus, with occasionally an underlying area of necrosed epithelium. The following day superficial necrosis of two-thirds the depth of the mucosa with leukocytic infiltration had occurred. Injection of bile and acid into the lumen of the stomach by a stomach tube or through the pylorus, during the period of digestion, caused excoriation, hemorrhagic infiltration and ulceration. He observed negative results in a stomach during fasting. After tying the esophagus and duodenum, he injected bile into the stomach for twenty-four hours; large quantities of bile alone caused hemorrhagic lesions; small amounts of bile with acid also caused lesions;

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114. Bolton, Charles: The Part Played by the Acid of the Gastric Juice in the Pathological Processes of Gastric Ulcer, J. Path. & Bact. **20**:133, 1916.

115. Butsch, J. L.: Ulcers of the Gastro-Intestinal Tract with Special Reference to Gastro-Jejunal Ulcers. Papers from The Mayo Foundation and the Medical School of the University of Minnesota, Philadelphia, W. B. Saunders Company, 1915-1920, vol. 1, p. 57.

116. Smith, G. M.: An Experimental Study of the Relation of Bile to Ulceration of the Mucous Membrane of the Stomach, J. M. Research **30**:147, 1914.

bile injected with a 5 per cent solution of sodium bicarbonate did not produce lesions except in one instance. He concluded that the presence of acid is necessary for the injury of the mucosa by bile. He quoted Rywosch as having produced inflammation and gangrene of the stomach of rabbits by feeding an excess of bile salt. Oddi and Dastre [117] did not get these results following cholecystogastrostomy. Smith concluded that it must be conjectured whether in man the bile may become a source of injury to the epithelium, particularly since it normally regurgitates through the pylorus into the stomach. Sellards [118] studied the effects of bile salts by injecting sodium glycocholate intraperitoneally. He produced large hemorrhagic areas in the stomach and ulceration of the mucosa. The subcutaneous injection of bile or bile salts produced similar lesions. Small repeated doses tended to localize ulcers near the pylorus. Since there were only a few minute lesions in the lungs and intestines, Sellards claimed for the bile salts a specific action on the gastric mucosa.

Such methods of studying the influence of the digestive juices are limited both in variety of experimental procedures and in the lack of control of physiologic reactions. Recourse must be had to surgical methods in order to determine the nature of the physiologic interrelationship of the juices. It is true that unphysiologic conditions may be established by such surgical measures, but as hepatectomy makes it possible to study the function of the liver and pancreatectomy to study the function of the pancreas, so the surgical procedures which have resulted in the formation of ulcer disturb the normal status (as nature may do with greater finesse), and produce effects which make it possible to analyze the significance of the juices from the point of view of formation of the ulcer.

Surgical Methods.—Kapsinow [119] excluded the bile from the digestive tract by implanting the fundus of the gallbladder into the pelvis of the right kidney (cholecystonephrostomy). When healing was complete he ligated and divided the common duct. The animals lost weight and refused food, and tarry stools developed. Necropsy was performed in two or more weeks. In seventeen of forty-three animals single or multiple ulcers from 2.5 to 5 cm. in diameter, with punched-out overhanging edges were formed. They extended to or perforated the serosa. Kapsinow quoted Whipple as having produced ulcer after ligating the

117. Oddi, R., and Dastre, A., quoted by Smith: J. M. Research **30**:147, 1914.

118. Sellards, A. W.: Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts, Arch. Int. Med. **4**: 502 (Nov.) 1909.

119. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, Ann. Surg. **83**:614, 1926.

common duct in the presence of a biliary fistula, but he criticized the work because of the possibility of infection ascending through the fistulous tract. Gundermann,[37] after simple ligation of the common duct, observed the same symptoms of hepatic dysfunction as after partial ligation of the portal vein, namely, cerebral, renal and gastroduodenal disturbances, the stomach and duodenum showing hemorrhages and ulcerations. Smith anastomosed the gallbladder to the stomach with and without ligation of the common duct, but results were negative in both instances. He reported negative results after the same procedure by Oddi and Dastre. Beaver,[120] likewise, did not observe ulcers following cholecystogastrostomy and ligation of the common duct. As stated, Greggio quoted Mueller, Köllicher, Bidder and Schmidt, Beati and others as having noted ulcers after exclusion of the liver. Bollman and Mann [38] reported that ulcers had perforated following partial hepatectomy, true Eck fistula and ligation of the common duct, procedures which probably influenced the quantity of bile entering the duodenum.

Little study has been made of the effect of excluding the pancreatic juice alone. Jona,[76] after tying the pancreatic duct in eleven animals, found ulcers of the duodenum, stomach and jejunum which he ascribed to lack of neutralization of the acid chyme. Gallagher [29] observed delayed healing of traumatic ulcers of the duodenum after ligation of the pancreatic duct.

The combined elimination of the bile and pancreatic juice has been studied thoroughly. Kehrer [121] implanted the pancreatic duct into the appendix or lower part of the ileum and anastomosed the gallbladder to the same site, ligating the common duct. In six animals that died at different intervals, he found marked injury to the wall of the stomach. Necropsy after thirteen, twenty-five and sixty-four days disclosed superficial circumscribed necrosis with deeper necrosis in three other dogs on which necropsy had been carried out after nine, twenty-five and 100 days. Macroscopically and microscopically, they were typical ulcers. Mann and Williamson [122] studied the production of ulcer in the duodenum, following transplantation of both the bile and the pancreatic ducts into the lower part of the ileum. The ulcers produced were single and multiple, indurated, varying from 1 to 3 cm., and were situated in the region between the pylorus and the ampulla of Vater.

Mann was the first to study the formation of ulcer following the entire elimination of all the duodenal alkaline juices. The historic development of his ideas show clearly the underlying factors in these studies.

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120. Beaver, M. G.: Personal communication to the author.

121. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwüres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:679, 1914.

122. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1922.

While investigating the problem of whether or not the duodenum produced a secretion essential to life, he devised a one-stage operation, excising the duodenum, anastomosing the jejunum to the transected pylorus and then implanting the pancreatic and bile ducts into the anastomosed jejunum. In two of ten dogs operated on, peptic ulcer resulted. Mann and Williamson then transplanted the bile and pancreatic ducts into the ileum, from 30 to 50 cm. from the cecum. Definite ulcers developed in ten of thirty-one animals (five ulcers were chronic). Removal of the duodenum and anastomosis of the jejunum to the pylorus, with transplantation of the bile and pancreatic ducts into the distal part of the ileum, resulted in ulcers in eight of the ten dogs operated on. The procedure was then simplified by devising the "duodenal drainage" operation. By this method the duodenum was isolated by transection at the pylorus and at the upper part of the jejunum. The pyloric end of the duodenum was closed in and the distal end anastomosed to the distal part of the ileum; the free end of the jejunum was anastomosed to the pylorus. With the duodenal alkaline juices drained into the ileum, the acid chyme of the stomach drained into an unprotected jejunum. Definite ulcers developed in fourteen of sixteen animals. They were usually situated a few millimeters from the gastrojejunal anastomosis. They developed usually within one or two months after operation, were from 4 to 15 mm. in diameter and penetrated to various depths. A gray covering first appeared over an area on the mucosa where killed, coagulated cells were present. Hemorrhage occurred between the adjacent tubules. As the mucosa disappeared, leukocytic infiltration developed, and the process penetrated the muscularis mucosae. Perforation occurred in from forty-eight to sixty hours, chronicity was established in three weeks, or the lesion was the same at the end of five months as at the end of one month.

In evaluating the factors involved in this result, Mann conceived of the acid chyme as being ejected through the pylorus by the gastric contractions, as if through a nozzle, and impinging forcibly against the wall of a segment of intestine containing little, if any, alkali; the mechanical and chemical action of this stream led to necrosis of the epithelium and the formation of ulcer.

The degree of acidity and the amount of acid to which the ulcer-bearing area is subjected depends normally on the balance at the pylorus between the gastric acid chyme and the alkaline secretions of the duodenum. The combined intestinal, pancreatic and biliary secretions must be sufficient to neutralize the acid chyme passing the pylorus to from 0.12 to 0.14 per cent, as shown by Boldyreff.[123] Mann showed that if,

123. Boldyreff, W.: The Self-Regulation of the Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1, 1915.

after a duodenal drainage operation, the duodenal juices were drained back into the jejunum just distal to the gastrojejunal anastomosis, so that such neutralization did occur in the ulcer-bearing region, a lesion did not develop. Morton similarly showed that secondary anastomosis of the closed duodenum to the jejunum after surgical duodenal drainage, so that alkalis drained back at the site of ulcer, led to the healing of an existing ulcer.

By several experimental methods, Morton [124] further confirmed the idea that the chemical and traumatic factors are of major importance in establishing chronicity in ulcers and failure to heal. He excised pieces of mucosa from the lesser curvature in dogs after the duodenal drainage operation, and showed persistence of the defect in from 50 to 62 per cent of those in the antrum after a period of two weeks. This was in contrast with normal controls, in which similar areas with excised mucosa healed in two weeks, with complete epithelization. Incidentally, after excision of mucosa from the greater curvature of the antrum in drainage operations healing was more rapid, showing that whatever the factors that prevented healing, they were more active on the lesser curvature. Finally, Morton transplanted jejunal patches with an intact circulation into several different areas in the gastric wall of dogs on which duodenal drainage had been performed. In thirteen cases, four ulcers developed on the patches. Again suggesting the greater activity of the destructive forces on the lesser curvature, three of these ulcers developed in patches on the lesser curvature, and only one on a patch elsewhere. This is in contrast with Morton's control studies (and corroborating earlier work by de Takats and Mann [125]), in which only one ulcer developed in jejunal patches on the lesser curvature and none on patches in other parts of the stomach in a series of normal dogs. The observations extended over a period of from thirty-six to 419 days.

Mann considered the active mechanical factor in the duodenum to be the force of the impinging stream ejected through the pylorus. In the stomach, Morton considered the mechanical factors chiefly active in localizing the ulcers as the paucity of protecting rugae in the prepyloric segment, particularly along the "Magenstrasse" with its poor blood supply, and the convergence of the lines of force along the lesser curvature, as suggested by Aschoff.[126]

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124. Morton, C. B.: Observations on Peptic Ulcer: IV. Patch Transplants of Jejunum in Stomach, Ann. Surg. **85**:879, 1927.

125. De Takats, Geza, and Mann, F. C.: The Effect on the Jejunal Mucosa of Transplantation to the Lesser Curvature of the Stomach, Ann. Surg. **85**:698, 1927.

126. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber Company, 1924, p. 358.

I. EFFECTS PRODUCED BY DRAINAGE OF THE DUODENAL SECRETIONS BACK INTO THE STOMACH: MECHANICAL FACTORS

The following report represents my work on peptic ulcer produced experimentally by the methods devised by Mann. The principle of the methods used by Mann and his co-workers consists essentially in shunting the alkaline secretions of the duodenum away from the pylorus so that the gastric juice and chyme are not neutralized. This has been accomplished by operations such as transplantation of the bile and pancreatic ducts into the distal part of the ileum, or by Mann's method of surgical duodenal drainage.

As stated in the preceding review, Mann and Williamson demonstrated the occurrence of ulcer in the duodenum in about 50 per cent of the dogs in which the bile and pancreatic ducts had been transplanted into the distal part of the ileum. Morton showed that, following surgical duodenal drainage, peptic ulcers formed in the anastomosed jejunum in approximately 100 per cent of experiments. He also found that, whereas in the normal dog traumatic lesions of the gastric mucosa healed readily, following a duodenal drainage operation such lesions tended to become chronic peptic ulcers. In a similar way he demonstrated a greater tendency toward ulceration of transplants of jejunal patches in the gastric wall in dogs subjected to duodenal drainage than was the case in normal dogs.

METHODS

In the present study the operation of surgical duodenal drainage was modified in such a way that while eliminating the alkaline secretions from the distal side of the pylorus they were shunted to the gastric side. This was accomplished by draining the duodenal secretions into the fundic portion of the stomach rather than into the distal part of the ileum. It was an apparent assumption that these alkalis might control the acid factors in the stomach and thus prevent the formation of the ulcers which developed after total elimination of the alkalis.

The same type of dogs used in the former studies were used in these experiments. All surgical procedures were carried out with the dogs under ether narcosis. Careful aseptic technic was observed throughout. Clamps were not used at the lines of anastomosis. Absorbable catgut was used for all intestinal suture work.

The abdomen was opened by a high median line incision. The pylorus was exposed and the vessels and nerves to the upper border were cut between two ligatures. The pylorus was severed, and the duodenal end was inverted. In like manner, the jejunum was severed just distal to the ligament of Treitz. The distal end was brought up and anastomosed to the open gastric end of the pylorus, thus reestablishing the continuity of the tract, with the duodenum excluded. The distal end of this isolated duodenum was anastomosed to the fundic portion of the stomach. This was done by end-to-side anastomosis, or by side-to-side anastomosis following closure of the distal end. These anastomoses were made on either the anterior or the posterior surface of the stomach. The type of anastomosis employed did not have any influence on the end-results of the experiment (fig. 1).

The modified technic of surgical duodenal drainage established a new type of disturbance of the relationship between the gastric chyme and the duodenal juices. The whole volume of duodenal alkalis, during their entire secretory cycle, was shifted from the distal side of the pylorus into the fundic portion of the stomach. These duodenal secretions were now retained in the upper part of the digestive tract, were freely intermixed with the gastric juice, and in this state passed through the pylorus into the jejunum (now unprotected by alkalis) and on into the intestinal tract (fig. 2). The significant question was: Could these alkalis which emptied into the stomach control the acidity of the gastric juice and thus prevent the formation of ulcers?

After operation, food was withheld for from two to three days. The dogs recovered quickly from the effects of the operation and were placed on routine kennel care. They were fed regularly with kennel food, and supplementary feedings of milk and syrup were given if they lost weight.

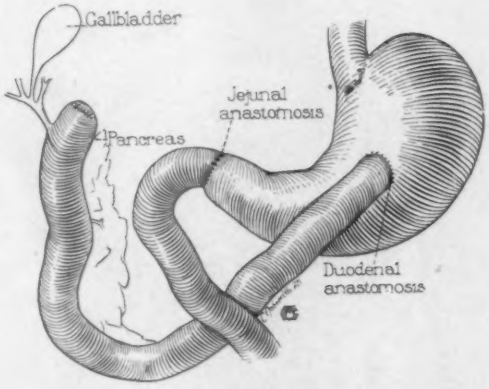

Fig. 1.—Operative procedure, showing the duodenum draining the secretions of the gallbladder, liver and pancreas into the fundic portion of the stomach.

RESULTS

Types of Ulcer.—Following the operation typical ulcers of the jejunum, such as were reported in all the earlier studies by Mann and his colleagues, formed in approximately 80 per cent of a series of twenty-six dogs. This figure is slightly lower than in the other series, which can be accounted for by the fact that two dogs were etherized because an ulcer was suspected; at necropsy, an ulcer was not found. Two other dogs in this series are still living two years after the operation, and the presumption is that ulcers have not developed. These four dogs have lowered the percentage of occurrence of ulcer.

The ulcers usually formed within from one to three months. Some of them perforated, causing sudden death. Others were first suspected when the dogs began to refuse food and lose weight. If the dogs were etherized at this time, ulcers of the anastomosed jejunum were usually found. The variations in the length of time in which the ulcers formed

preclude the possibility that operative trauma, thrombosis of vessels or cachexia are the essential factors concerned in producing these lesions.

Usually single, but sometimes multiple, ulcers were found. They were situated just beyond the suture line, and were usually regressive up to the gastric mucosa. If they were multiple they were distributed over an area of from 5 to 7.5 cm. of the upper part of the jejunum. The acute ulcers were cleanly punched out, suggesting a rapidly progressing type of lesion. The three layers of the intestinal wall, the

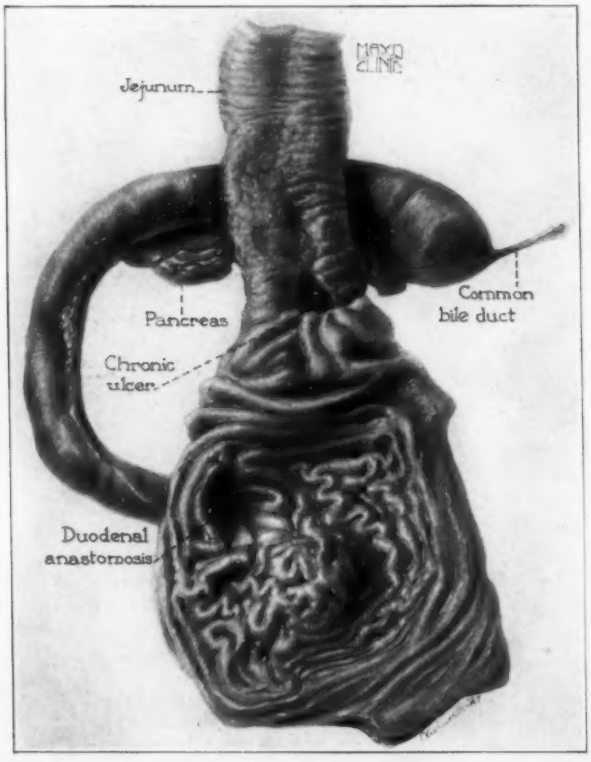

Fig. 2.—Anastomosis of the distal end of the duodenum to the fundic portion of stomach, thus draining the alkalis into this segment. The gastric chyme with the duodenal alkalis intermixed empty into the unprotected jejunum. A chronic ulcer appears at the usual site of formation.

mucosa, muscularis and serosa, were all extensively involved. Even these ulcers were not truly acute, in that the edges of the lesion were slightly indurated, suggesting some of the tissue reaction responsible for chronicity in other specimens (fig. 3).

The subacute ulcer, which was the type most frequently seen, gave definite evidence of early chronicity. The edges of the crater were thickened, due to the round cell infiltration from the tissue reaction.

There was graded involvement of the three coats in a terraced manner. The mucosa was ulcerated most extensively, its edges indurated, rounded and overhanging. The muscularis was eroded less widely, and the serosa least of all. The occurrence of ulcers, without contact at the suture line,

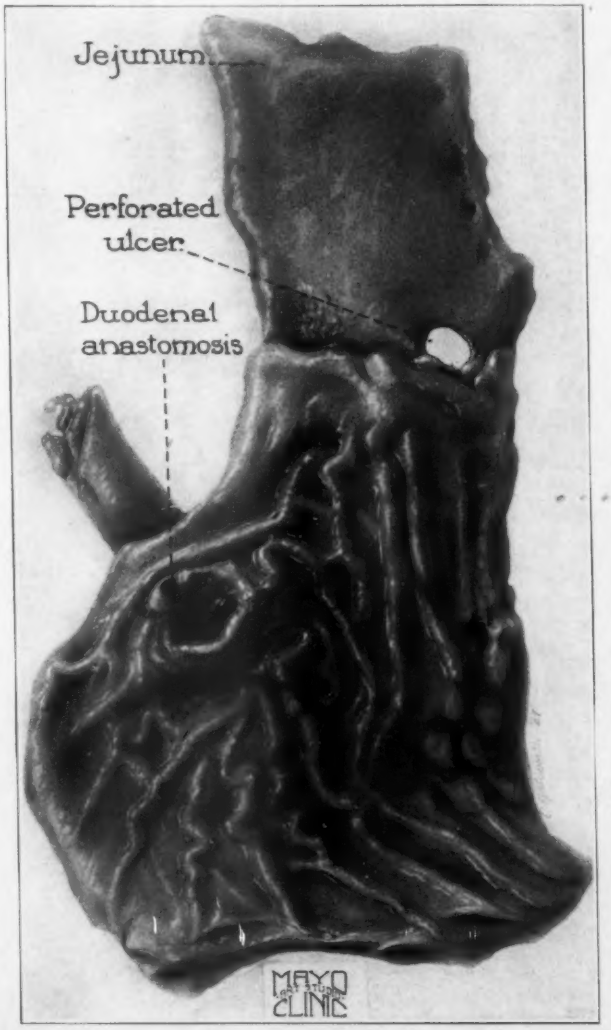

Fig. 3.—Acute ulcer of the jejunum following surgical duodenal drainage. Encroachment on line of anastomosis, with gastric mucosa intact.

indicates that the ones which encroach on the suture line are regressive (fig. 4).

The chronic indurated ulcers possessed all the characteristics of the crater type of ulcer observed in man. They were of considerable depth,

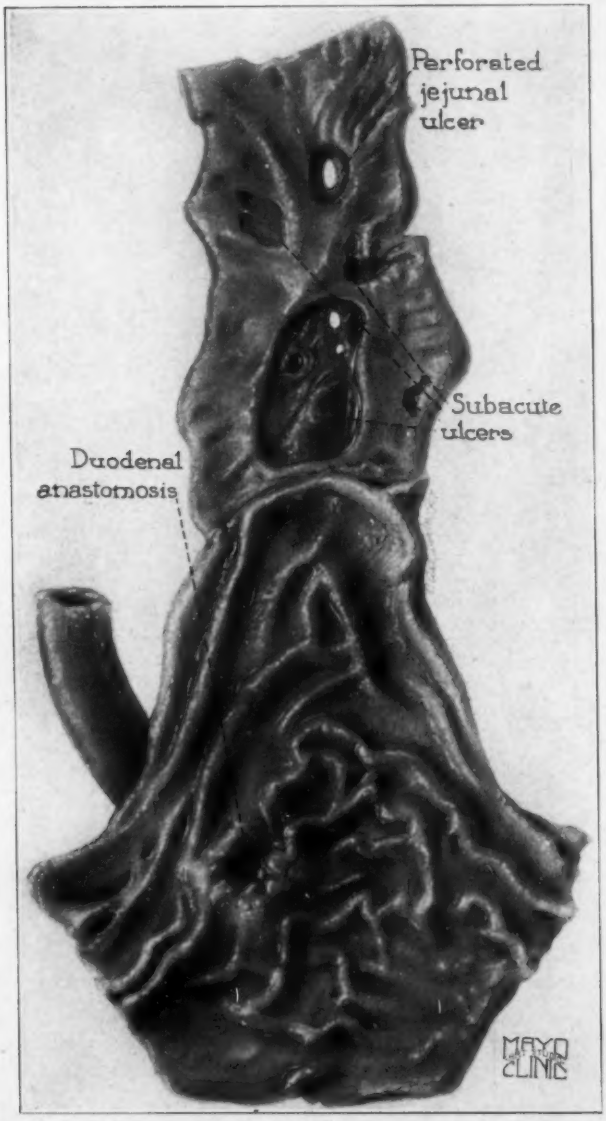

Fig. 4.—Subacute types of ulcer with less extensive ulceration of underlying muscularis and serosa than of the mucosa. Ulcers at considerable distance from line of anastomosis.

from 6 to 10 mm., with sloping indurated walls. The mucosa was thickened and overhung the sloping walls. The base of these chronic ulcers was usually formed by the peritoneal surface of an adjacent organ, such as the liver, onto which they had slowly perforated. This slow perforation afforded the tissues an opportunity to establish a more intense reaction which is characteristic of chronicity, that is, round cell infiltration and fibrosis (fig. 5).

Mechanical Factors.—The basis for the production of these experimental ulcers has been attributed mainly to the mechanical and chemical factors involved in the physiologic functions of this region. Two of the specimens in this series presented significant evidence of the influence of

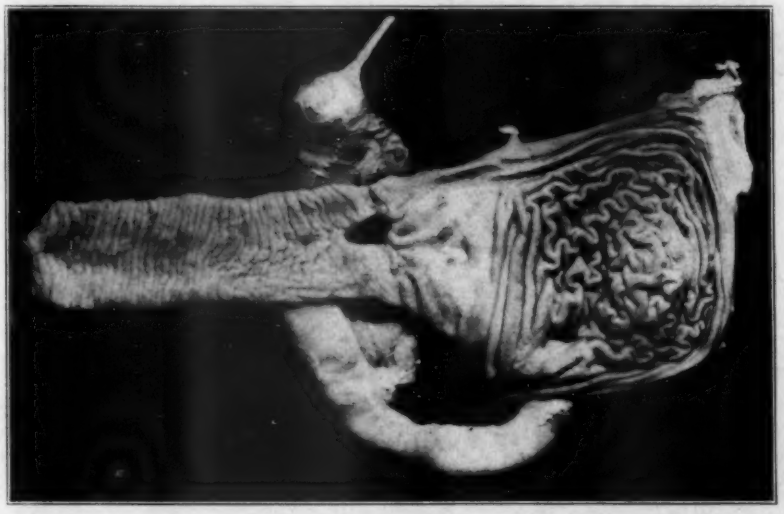

Fig. 5.—Typical chronic indurated crater type of ulcer. Small perforation in base of ulcer was penetrating onto lobe of liver, which saved the animal from death by perforation.

the two mechanical factors involved: the force of the stream ejected through the pylorus and the friction of coarse cellulose foods.

In the first specimen, a chronic peptic ulcer about 6 mm. in depth was present; fifty or more hairs from the dog's hide were embedded in the sloping wall of the distal half of the crater. There were only one or two hairs in the proximal half of the ulcer. Apparently, the chyme was ejected through the pylorus and impinged on this segment of the intestine with force sufficient to embed the hairs in the wall of the ulcer. This, of course, is not controlled proof, but it is suggestive evidence of the mechanical factor established by the passage of chyme from the stomach (fig. 6).

The other mechanical factor, the destructive friction of coarse cellulose foods on the delicate granulations and epithelial cells of a heal-

ing ulcer, was strikingly illustrated by the second specimen. The dog died suddenly from a perforated ulcer. At necropsy the peritoneal cavity did not show gross peritonitis. In the jejunum, just distal to the suture line, was a perforated ulcer through which protruded about 0.3 cm. of the tip of a moderate-sized pyramidal piece of turnip, a constituent of the mash fed to the dogs. The jejunum was carefully opened so as to leave the piece of turnip undisturbed. The lumen of the bowel and stomach contained a considerable quantity of bloody fluid, all of which was retained within the lumen of the viscera, because the ulcer had

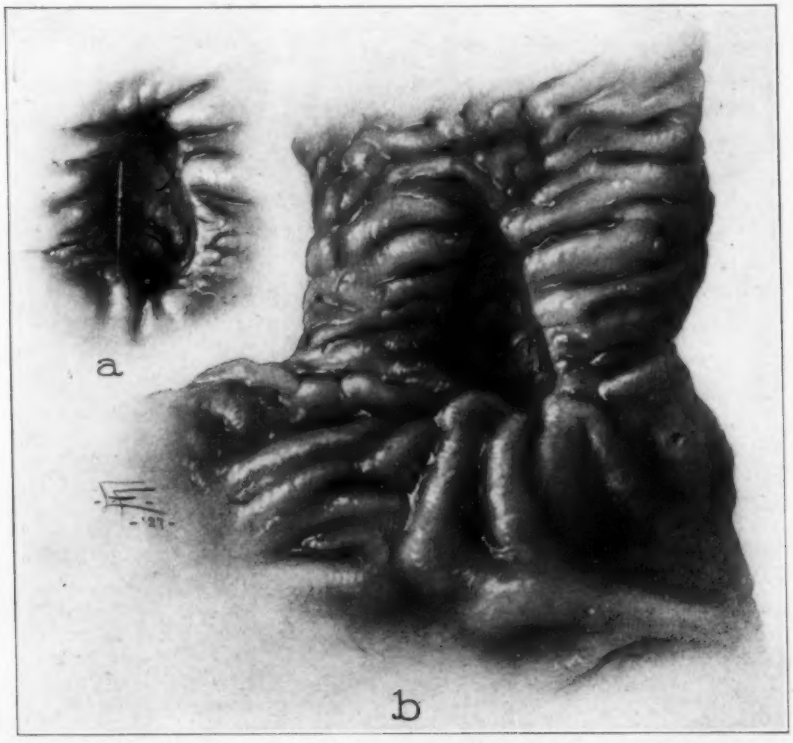

Fig. 6.—*a*, absence of hairs in proximal end of ulcers; *b*, hairs embedded in the distal half of the crater of the ulcer.

been completely occluded by the turnip which had perforated it. This perforation of an ulcer represents a most extreme degree of destruction by the friction of food (figs. 7 and 8).

COMMENT

In the early studies by Mann and his colleagues in which the original method of surgical duodenal drainage had been used, ulcers were produced by entirely eliminating the alkalis from the pyloric region and exposing the segment beyond the pylorus to the full autolytic action of

the gastric chyme. In the present studies the alkalis are still retained in the upper part of the intestinal tract but proximal to the pylorus; this allowed the uncontrolled autolytic action of the gastric chyme to persist beyond the pylorus. The resulting lesions indicated that one rôle of the alkalis, in the normal physiologic relationship, is to prevent the

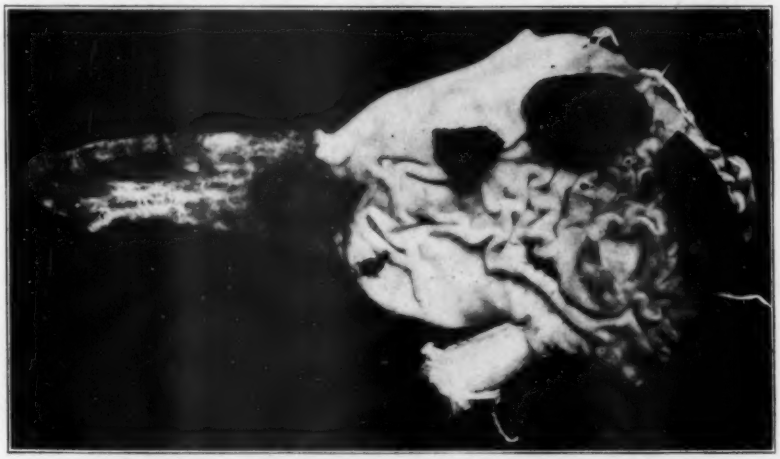

Fig. 7.—Piece of turnip perforating an ulcer, just distal to the pylorus; other pieces of turnip were free in the cavity of the stomach.

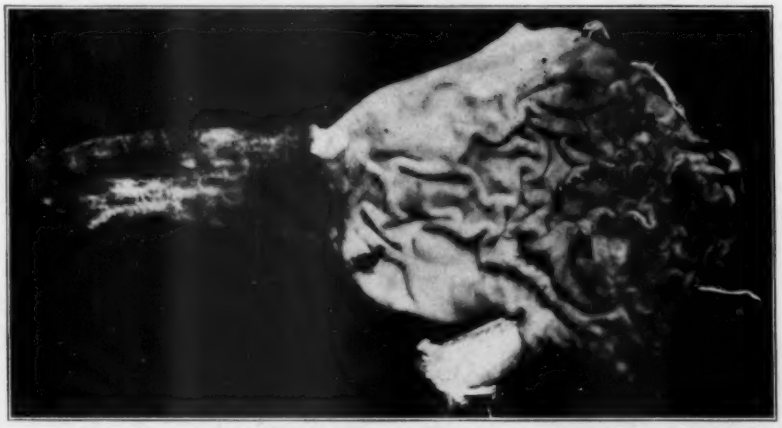

Fig. 8.—Same specimen as that shown in figure 7. Perforated type of ulcer revealed when the piece of turnip was removed. Discoloration of the bowel points to evidence of hemorrhage.

formation of ulcer, not by any specific protective action, but by some type of buffer or diluting action beyond the pylorus that terminates the acid peptic activity of the gastric chyme.

The results of these experiments emphasize the importance of the mechanical factors in causing chronic peptic ulcers. The specimen in

which the hairs from the dog's hide were found embedded in the distal half of the ulcer constitutes an observation just as suggestive as if particles of carbon had been mixed with the dog's food and these had been observed in the wall of the ulcer. The specimen indicates the force with which the stream ejected through the pylorus impinges on the site of ulcer formation.

The destructive action of coarse cellulose food is apparent when the delicate mechanism involved in the healing of an ulcer is considered. Morton, summarizing the experimental work done on the healing of ulcer, stated that Mann observed:

> The base of the lesion is first cleaned, the slough separates, and a protecting coat of serum and coagulum forms over healthy granulations. These processes ordinarily take about four days. Simultaneously the mucosa begins to grow out from the edges as a thin layer of flat epithelial cells. The edges of the mucosa tend to overhang and the granulations to push up in the center, so that the growing edge of mucosa is protected in the resulting depression. This initial stage which has the effect of also decreasing the area to be healed over takes place in about ten days. Once initiated, the healing, if undisturbed, is rapid. In twenty days three-fourths or more of the base is covered with epithelium, and in thirty days the lesion is usually healed entirely. The scarring is in many cases hardly noticeable.

How easily this delicate mechanism might be compromised by the influence of friction was suggested by the piece of turnip which had perforated an ulcer. If a large piece of cellulose food could exert so destructive an influence, it is reasonable to assume that cellulose food of varying degrees of coarseness would exert a graded amount of friction, thus continually aborting the reparative tendencies of an ulcer.

That the assumption is justified is borne out by the experience of Bollman and Mann with dogs on whom an Eck fistula had been made. In a considerable percentage of the dog's acute perforated ulcers of the duodenum developed while they were fed on coarse food which contained much cellulose material. When the coarse foods were replaced by a soft or liquid diet, the occurrence of ulcers was decreased. This observation affords control evidence that with a partial deficiency (qualitative or quantitative) of the bile in the duodenum, the presence or absence of coarse cellulose food was the important factor in determining the frequency of the formation of ulcers in the duodenum.

On the gastric side of the pylorus there are two factors which would augment the friction of coarse cellulose food in the prepyloric segment, and thus greatly influence the localization of ulcers in this segment, as occurs clinically, and as reported in Morton's experiments. The first factor, as Morton pointed out, is the anatomic arrangement of the mucosa in this segment, which is closely attached and does not form protective rugae such as are found in the fundic portion of the stomach. This is particularly true of the lesser curvature. It is interesting to note

that there is total absence of such rugae in the duodenum and jejunum, which are most subject to ulceration and would thus permit maximal friction by coarse cellulose food.

The second and probably a highly important factor in augmenting the friction of cellulose food in the stomach is the type of motor activity in the prepyloric segment which I observed while working with the test meal of meat. In response to this adequate stimulus, the whole prepyloric segment was thrown into vigorous tonic contraction, so that it appeared sausage-shaped. Frequent peristaltic waves traversed the segment during early digestion, being superimposed on this tonic contraction. In contrast to this activity, the fundus appeared like a big motionless ball, with a simple wavering around its periphery. Pieces of cellulose food caught between the approximated, vigorously contracting walls of the prepyloric segment might exert considerable destructive friction on the reparative granulations and epithelial cells of an ulcer. If these particles were rejected at the pylorus and driven back into the fundus, as indicated by Cannon's study, the friction of each particle might be multiplied many times.

SUMMARY OF STUDY I

In this study, the technic of surgical duodenal drainage was so modified that the alkaline secretions of the duodenum were shunted from the distal side of the pylorus into the fundic portion of the stomach. Despite the volume of alkalis drained into the stomach, ulcers still formed in the anastomosed jejunum in approximately 80 per cent of the experiments.

Evidence was obtained which substantiated Mann's interpretation of the important mechanical factors that are active in causing these experimental ulcers, and which probably influence the localization of clinical ulcers. On the duodenal side of the pylorus these are the result of the force of the impinging stream ejected through the pylorus, and of the destructive friction of coarse cellulose foods on the reparative granulations and epithelial cells of a healing ulcer. On the gastric side of the pylorus there is the same friction of coarse cellulose food augmented in the prepyloric segment by the absence of protective rugae, particularly on the lesser curvature, and by the vigorous tonic and peristaltic contractions of this segment which appear in response to an adequate meal.

II. THE CHEMICAL FACTORS IN EXPERIMENTALLY PRODUCED PEPTIC ULCER

The present study was an investigation of the chemical factors involved in the development of the peptic ulcers produced by the experimental procedures devised by Mann. Former experiments have indicated fairly definitely the mechanical factors which influence the

development and localization of the ulcers. The active chemical factors have been suggested by the nature of the disturbed physiologic function. The rationale of the methods is best indicated by Mann's own words:

> Our results in a preliminary series of experiments in which acid was administered orally, as well as the results of previous investigators, demonstrated that simulating the so-called "hyperacidity" and "hypersecretion" by the artificial administration of acid would be very difficult. The upper part of the intestinal tract can be subjected to an acid medium just as effectually by injuring the alkali-producing mechanism as by the administration of acid. We, therefore, undertook to eliminate singly and in combination, the various constituents of this mechanism, and it was found that injury of any one of these constituents caused the development of typical chronic peptic ulcer in a small percentage of experiments. We finally devised a method which consisted essentially in draining the alkaline secretion which is poured into the duodenum, into the ileum at a considerable distance from the point of emergence of the acid from the stomach into the intestine. Following this procedure, a typical peptic ulcer developed in a high percentage of experiments.

These ulcers, he thought, resulted from a disturbance of the normal relationship between the gastric and duodenal juices beyound the pylorus, besides the mechanical factors of that region.

The nature of this disturbed relationship between the gastric and the duodenal juices has never been exactly determined. Mann showed that an acid reaction to litmus persisted far down the intestinal tract following surgical duodenal drainage, whereas normally the reaction is alkaline to litmus. This was the basis of his idea that the acid chyme which passed the pylorus was not neutralized and acted as a major factor in the development of these ulcers.

Two hypotheses suggest themselves as to the nature of the disturbed relationship of the secretions resulting from this procedure. First, if Boldyreff's theory is accepted that the acidity of the gastric juice is regulated by regurgitation of duodenal alkalis into the stomach, then these procedures would injure this mechanism so that the mucosa would be exposed constantly to highly concentrated acid. This persistent state of hyperacidity might account for the production of the ulcers. If this theory is not true and the acidity of the gastric contents is independent of regurgitation of the duodenal alkalis, then the second hypothesis is probable, namely, that the acid peptic activity of normal gastric chyme causes these ulcers, because its action is not terminated beyond the pylorus following the loss of diluting or buffer secretions, bile and pancreatic juice. It is important to know which hypothesis is true, because, if it is the second one, these experiments have demonstrated the highly destructive action of the normal gastric chyme under experimental conditions which allow it to ulcerate the mucosa.

METHOD

By a method of fractional gastric analysis that I devised [127] for use on the normal dog it is possible to measure the effect of these procedures on the chemical changes of the gastric contents during digestive activity and during rest. This method, which I shall report in more detail elsewhere, consists in feeding a fasted animal with a meal of meat and water. Half an hour after feeding, single specimens are aspirated every thirty minutes until free acid appears. Then the aspirations are made every fifteen minutes until the free acid is neutralized. Chemical determinations are made for total and free acids, and these are charted. The total chlorides are titrated, and the chlorine value of the free acid deducted, so that the resulting figure, which is charted, indicates the chlorine value in neutral or combined form.

Three groups of dogs were operated on so as to repeat the methods used in the whole series of studies by Mann and his colleagues. Studies with the fractional

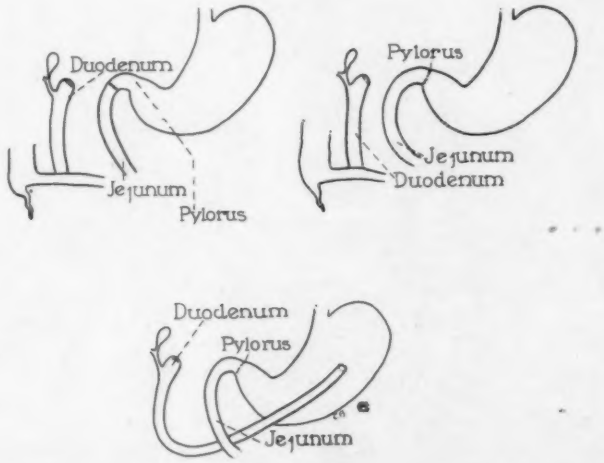

Fig. 9.—Three types of operative procedures: modified surgical duodenal drainage with section in first portion of duodenum; surgical duodenal drainage with section at pylorus; surgical drainage of duodenal alkalis into fundic portion of the stomach.

test meal of meat were made before and after the operations. The three procedures were as follows (fig. 9):

1. *Modified Surgical Duodenal Drainage.*—The usual type of drainage operation was modified by sectioning the first portion of the duodenum at the middle, rather than sectioning the pylorus. The duodenojejunal flexure was sectioned beyond the ligament of Treitz. The proximal end of the duodenum was closed in, and the distal end was anastomosed to the distal part of the ileum. Duodenojejunal anastomosis was made beyond the pylorus after the lumen of each segment had been enlarged by a longitudinal incision, thus obviating any mechanical dysfunction from stenosis at the line of anastomosis. Furthermore, nerves or significant blood vessels were not severed in the procedure.

127. McCann, J. C.: Unpublished data.

2. *Surgical Duodenal Drainage.*—The original method was used for this group. The nerves and vessels to the upper border of the duodenum were cut between ligatures. The pylorus itself was severed and the usual anastomoses made: the jejunum to the pylorus, and the closed duodenum to the distal part of the ileum. Thus all the disturbances of motor function present in the early studies as a result of the manipulations at the pylorus were present in this group.

3. *Surgical Duodenal Drainage Back into the Stomach.*—The technic was the same as that reported in the preceding study. The pylorus was severed and the duodenal end inverted. The duodenojejunal flexure was severed just distal to the ligament of Treitz. The distal end of the jejunum was anastomosed to the open gastric end of the pylorus. The distal end of the isolated duodenum was anastomosed to the fundic portion of the stomach. Thus the whole volume of duodenal alkalis was shifted from the distal side of the pylorus into the fundic portion of the stomach.

RESULTS

In the first procedure, since the duodenum rather than the pylorus was severed, all impediments to normal emptying were avoided. As

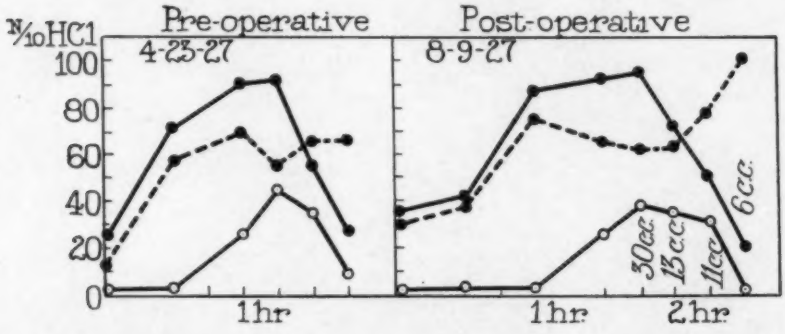

Fig. 10.—Chronic ulcer; the same essential character of curves occurred in response to a test meal before and after the surgical drainage of the duodenal alkalis from the pylorus into the distal part of the ileum; anastomosis in the middle of the first portion of the duodenum. In this and the following charts, the solid line with the hollow circles indicates the free hydrochloric acid; the solid line with the solid circles, the total acid, and the broken line with the solid circles, the combined chlorine.

shown in figure 10, there was no essential alteration in the character of the curves in response to the test meal whether the alkalis on the distal side of the pylorus were present or absent. There was the same preliminary rise in the total acid and combined chlorine curves. Subsequently, there was the same increase in the free acid value followed by a decrease to the point of complete neutralization. This final drop in the free acid value was accompanied by a terminal rise in the combined neutral chlorine value whether the duodenal alkalis were present or absent (fig. 10). This procedure was associated with the production of ulcers in the anastomosed jejunum, as occurred in all the experiments with the original type of duodenal drainage operation.

In the second procedure, using the original type of surgical duodenal drainage, fractional gastric analysis showed that the operative procedure had established an impediment to normal emptying. The essential character of the curves was the same before and after operation. The postoperative studies, however, revealed marked retention of the acid chyme in the stomach at the end of the cycle. In the normal dog the stomach was completely empty shortly after the appearance of free acid. During the period when free hydrochloric acid was present, decreasing quantities of juice, from 30 to 5 cc., were aspirated every fifteen minutes until neutralization was attained. After this type of operation, the stomach remained distended with fluid for a prolonged period, 230 cc. of acid chyme being drawn off late in the free acid period in one instance (fig. 11). After this procedure, Morton observed the change of acute traumatic lesions of the gastric mucosa into chronic peptic ulcers. As

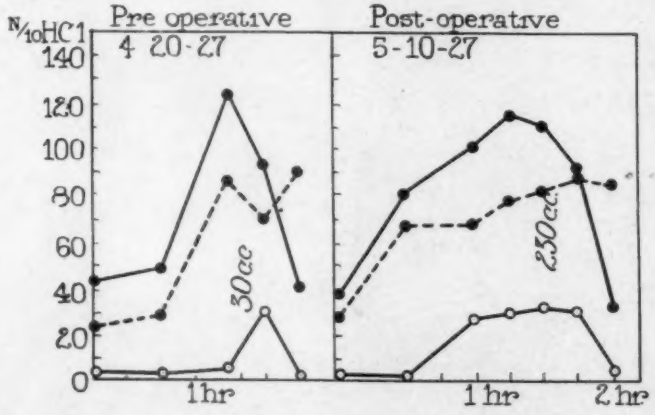

Fig. 11.—Duodenal drainage, late retention of chyme with anastomosis performed at the pylorus, with consequent prolonged exposure of traumatic lesions to normal acid peptic activity.

traumatic lesions healed in the normal dog, the formation of these ulcers was associated with prolonged exposure of the lesion to normal acid chyme.

In the third procedure the alkaline secretions of the duodenum were drained back into the fundic portion of the stomach, as described in the preceding study; the usual types of peptic ulcers were formed in the anastomosed jejunum in a high percentage of experiments. The results of the fractional studies in this procedure are significant as they show the persistence of acid peptic activity after the introduction of duodenal alkalis into the stomach.

Postoperative fractional test meals on three dogs revealed the usual characteristic curves of normal digestion, with average normal values

for free acid at the end of the period; namely, values of from 20 to 30 expressed in terms of cubic centimeters of tenth-normal sodium hydroxide. Figure 12 shows the same preliminary rise in the value of the total acids and neutral chlorides, followed by the usual type of curve for free acid. There was the terminal rise in the value of the neutral chlorine in both instances, before and after operation.

Two other phenomena were observed which may have some influence on the development of these ulcers. One was the elevation of the rate of the basal secretion of acid, and the other, the influence of hemorrhage on secretion.

Basal Secretion of Acid.—During the period when the dogs were eating poorly and they had lost considerable weight, presumably the stage of ulcer development, an increased quantity of the resting basal

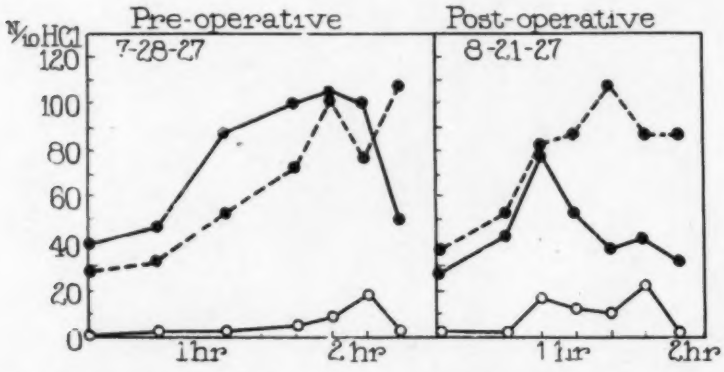

Fig. 12.—Perforated ulcer; the same character of curves was observed before and after surgical drainage of duodenal alkalis (gastric) into the fundic portion of the stomach.

secretion developed suddenly. The usual response to the test meal was observed, but following the completion of the digestive cycle a continuous secretion of juice of considerable acidity persisted (fig. 13). This change was not related in any way to a disturbance of the duodenal secretions because it was observed in dogs in which the alkalis drained into the distal part of the ileum, in those in which the alkalis were drained back into the stomach, and also in those in which gastrojejunostomy has been performed. This increased secretion was induced in a normal dog by a fast of seventy-two hours. It is probable that the phenomenon is related to this normal physiologic response to food after a prolonged fast, in which a high basal secretion is continued long after the digestion of a meal is complete.

Hemorrhage.—The other phenomenon was the association of hemorrhage with high acidity. Blood was aspirated from the stomach of three

dogs. In the first dog there was an absence of acid during a study of the stomach while fasting, and suddenly blood was present as the result of trauma. Immediately afterward, acid of considerable concentration appeared (50 tenth-normal hydrochloric acid). From a second dog 30 cc. of coffee ground material was obtained on a single aspiration of the stomach while fasting, with a free acid value of 60 tenth-normal

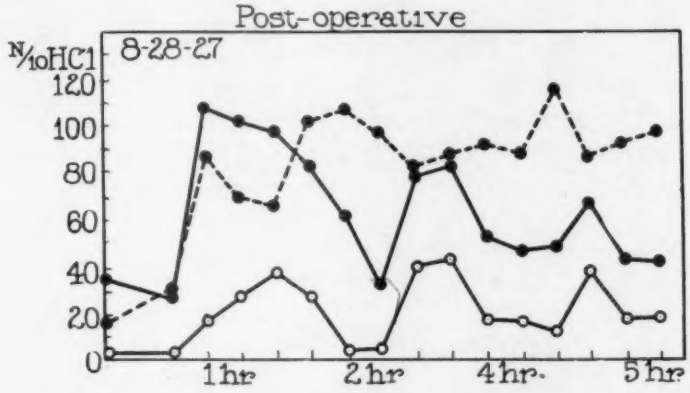

Fig. 13.—Duodenal drainage; continuous secretion of free acid after the completion of the normal response to a test meal (at two hour point) in a cachectic, ulcer-bearing dog.

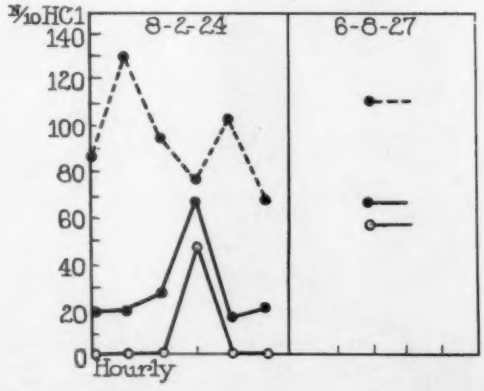

Fig. 14.—Hemorrhage (isolated); first specimen: single appearance of blood and free acid during a course of hourly aspirations; second specimen: single aspiration of coffee ground contents of high acid value.

hydrochloric acid (fig. 14). In a third dog continuous bleeding occurred for the major portion of a twenty-four hour period of fast. There was a definite relationship between the appearance and disappearance of blood and the concentration of the free acid of the gastric contents (fig. 15). It is difficult to judge how much a high basal rate of secre-

tion, as mentioned, may have been responsible for this continuous secretion, but the three observations suggest strongly that blood may act as an adequate stimulus to the secretion of hydrochloric acid.

COMMENT

These studies show that in all the procedures used to produce experimental ulcers, the chemical characteristics of the gastric contents are unaltered. Whether the duodenal secretions beyond the pylorus are partially or wholly removed, or whether they are shunted from the duodenal to the gastric side of the pylorus, the concentration of the acid of the chyme that passes the pylorus remains constant. Consequently, all these ulcers have occurred with the passage of chyme of normal acidity by the pylorus into a segment of intestine where their action is not

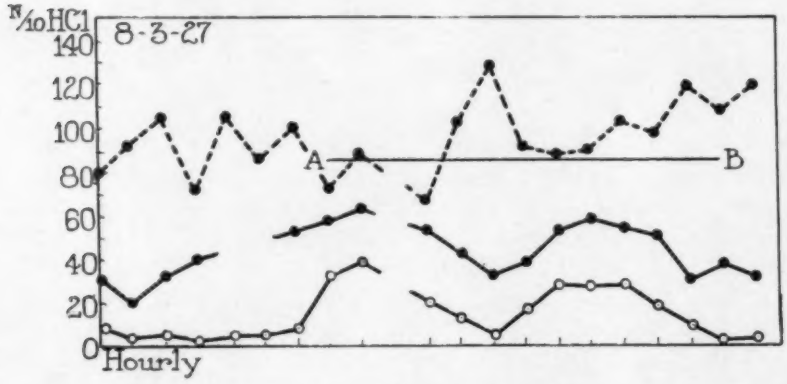

Fig. 15.—Continuous presence of blood in gastric contents aspirated hourly, from *A* to *B*, associated with persistent free acid.

terminated by the duodenal alkalis normally present on the distal side of the pylorus.

This constancy of the chemical constituents of the gastric contents, whatever the degree of disturbance of the alkaline factors on the distal side of the pylorus, is not in accordance with Boldyreff's theory of the control of gastric acidity by regurgitation of these alkalis. Whether part or all of the duodenal secretions are eliminated, there is no tendency toward a condition of hyperacidity in the stomach. There is the same adequate control of the acidity of the gastric juice, without evidence of a compensatory mechanism. Hence it would appear that there is a mechanism for the control of the acidity which is entirely intragastric and wholly independent of the regurgitation of duodenal alkalis back into the stomach, and that these experimental ulcers have resulted from the acid peptic activity of normal chyme which was not terminated beyond the pylorus because of the absence of neutralizing alkalis.

As established by the results in the first procedure, the ulcers which developed beyond the pylorus in a moderate percentage of instances following ligation or transplantation of the bile or pancreatic ducts singly, partial hepatectomy and Eck fistulas are dependent on the action of normal gastric chyme, and a partial deficit of the duodenal juices. These ulcers have been produced in a much higher percentage of experiments by establishing a complete deficit of the alkalis beyond the pylorus following transplantation of both ducts, or by doing surgical duodenal drainage. With a gradually increasing acid peptic activity beyond the pylorus, due to the constancy of the chemistry of digestion and the decreasing amount of alkali beyond the pylorus from these procedures, there is a directly increasing tendency to the formation of ulcers. In other words, there appears to be a graded tendency toward the formation of ulcer, directly proportionate to the alkali deficit beyond the pylorus.

Seeking a possible clinical application of these purely experimental facts, it is interesting to speculate whether clinically: (1) duodenal ulcers might result from a deficit of alkali on the distal side of the pylorus associated with disease of the liver, pancreas or gallbladder, which allows the acid peptic activity of the chyme to be sufficiently uncontrolled so as to ulcerate the duodenal mucosa; (2) hypersecretion and hyperacidity of juice of 95 tenth-normal hydrochloric acid might be uncontrolled by the normal quantity of alkaline secretions in the duodenum and thus produce ulcers, or (3) the immunity of the mucosa of the first portion of the duodenum can be lowered by such a mechanism as the toxins of a burn, or the localization of streptococci, so that it becomes susceptible to the degree of acid peptic activity which persists normally in the first portion of the duodenum before the chyme is completely neutralized by the alkalis of the duodenum, and is ulcerated by it.

In the second procedure an extraneous factor has been introduced, whether from nerve injury or from some degree of stenosis of the pylorus associated with end-to-end anastomosis. This factor acts as an impediment to normal emptying. Consequently, the mucosa of the stomach is exposed to normal acid peptic activity for a prolonged period. This fact establishes the basis of Morton's experimental gastric ulcers. He showed that traumatic lesions of the gastric mucosa, which healed rapidly in the normal dog, tended to develop into chronic gastric ulcers after surgical duodenal drainage. He also observed by roentgenologic study that there was slight gastric stasis during the first two weeks, and that this subsequently increased. These fractional test meal studies have shown that whereas traumatic lesions of the gastric mucosa tend to heal readily when exposed to normal acid peptic activity for a normal period, when exposed to normal acid peptic activity for a prolonged period as a result of stasis they tend to change to chronic peptic ulcers. Since the

only demonstrable variable following this operation is this prolonged exposure of the lesion to normal acid peptic activity, it is probable that the destructive activity of acid pepsin over a long period was responsible for the development of these gastric ulcers. This concept is in accord with Hughson's conclusions when he showed, after a series of roentgenologic studies on the emptying of the stomach, that in animals in which delay is demonstrated ulcerations remain active at least twice as long as in the group in which emptying is more rapid.

The demonstration that experimental gastric ulcers are associated with prolonged exposure to the normal acid chyme suggests hypothetic conditions that might lead to the development of gastric ulcers in clinical cases. A traumatic lesion of the gastric mucosa, associated with pylorospasm and prolonged retention of the fluid chyme of normal digestion, might result in a gastric ulcer. With lowered immunity of the gastric mucosa, for a prolonged period of time, by such an agent as the localization of streptococci, the normal acid peptic activity of digestion, together with the mechanical factors of the region, might initiate a lesion and produce a chronic peptic ulcer.

The persistence of normal values for acid in the third procedure, despite the drainage of all the duodenal alkalis into the fundic portion of the stomach, is an unexpected observation which may possibly be explained by an increase in the amount of acid secreted, to compensate for these alkaline juices. Whatever the explanation, the question is raised as to whether the favorable results following gastro-enterostomy for clinical ulcers may be due not so much to the neutralizing effect of these juices as to the mechanical drainage of the free acid aliquot which terminates the digestive cycle. It may be that, with the relaxed state of the musculature at the end of digestion, all the final free acid which usually coincides with the period of distress may drain through the relaxed stoma and thus spare the ulcer from its destructive action. This result supports the idea that normal acid pepsin, acting in the absence of an effective neutralizing mechanism, is the probable cause of these experimental ulcers. They are not due to the loss of any specific protective activity of the juices other than chemical, because, in this third procedure, all the duodenal alkalis are present at a point proximal to the site of ulcer formation where they do not alter the normal chemistry of digestion, and are displaced only from the point of effective neutralization in the duodenum.

Experimental data support the clinical impression that hemorrhage may stimulate the secretion of an amount of acid that will have a deleterious effect on an ulcer. Likewise, a high rate of basal secretion of acid may develop which will be equally harmful to an ulcer.

Since it has been shown that normal acid peptic activity is the chemical factor associated with the production of these experimental ulcers,

one fact is revealed which is of major clinical significance: the graded immunity of the upper intestinal tract to the destructive action of the gastric juice, or, conversely, the increasing vulnerability of the mucosa to the formation of ulcer as the distance from the cardia of the stomach increases.

Under the mechanical conditions of these experiments the gastric mucosa did not ulcerate from exposure to the normal autolytic action of the juice for normal periods of time. Even traumatic lesions in all parts of the mucosa healed when exposed to acid pepsin for the normal periods of digestion. Furthermore, the inherent immunity of the mucosa to this action is so marked that it never ulcerated spontaneously from prolonged exposure to this activity as resulted from surgical duodenal drainage. Even with prolonged exposure to this autolytic activity after surgical duodenal drainage traumatic lesions in the cardia healed successfully. Similar lesions in the prepyloric segment, which is the site of clinical formation of ulcer, developed into chronic ulcers from this prolonged exposure; but here there are also mechanical factors involved which tend to prevent the healing of such lesions.

The duodenal mucosa ulcerated spontaneously from exposure to unneutralized acid chyme of normal digestion (in the absence of alkalis after surgical duodenal drainage) in a fair percentage of experiments. The jejunal mucosa ulcerated in practically all instances when exposed to this activity under the same experimental conditions. The contrast between the immunity of the gastric mucosa and the susceptibility of the duodenal mucosa to spontaneous ulceration probably explains the clinical preponderance of duodenal over gastric ulcers in a ratio of four to one, provided the initial lesion is established as frequently in the stomach as in the duodenum. This gradient of immunity would also explain the tendency for gastrojejunal ulcers to form in the relatively unfavorable environment of gastrojejunostomy, the low percentage of occurrence being dependent on unrecognized factors.

It is not necessary to postulate a state of hyperacidity to explain the formation of chronic ulcers. They have resulted experimentally from exposure to normal acid pepsin for the remarkably short periods of normal digestion, under proper experimental conditions. It is probable that, since meat is progressively disintegrated to a fluid state by acid in combined form during early digestion, the devitalized cells of an ulcerating lesion may be somewhat susceptible to the action of this combined acid and pepsin of early digestion. Probably the action is not so marked as from the free uncombined acid of late digestion.

SUMMARY OF STUDY II

In a long series of experimental studies, Mann and his co-workers have produced typical peptic ulcers by injuring the neutralizing mechanism in the duodenum, so that the acid chyme from the stomach

could act on the mucosa without hindrance. In earlier studies I found that the mechanical factors active in producing these ulcers, and presumably influencing clinical ulcers, were the force of the stream ejected through the pylorus, the friction of coarse cellulose food and the vigorous motor activity of the preplyoric segment.

Using a method of fractional gastric analysis which I devised for use on the dog, the underlying chemical factor in the production of these ulcers was shown to be normal acid peptic activity. The ulcers produced exhibit the highly destructive character of the gastric chyme. Of great significance is the gradient of immunity of the mucosa of the intestinal tract to ulceration, which probably is the deciding factor in determining the greater frequency of duodenal ulcer as compared to gastric ulcer, and the tendency for jejunal ulcer to develop following gastro-enterostomy.

These studies demonstrate that the gastric mucosa possesses considerable immunity to the autolytic activity of the acid and pepsin secreted by the stomach, whether exposed to it for a normal period or for a prolonged period, because spontaneous experimental ulcers of the chronic type produced in these experiments never developed in the stomach. Likewise, the normal duodenal mucosa is completely immune to this activity under the condition of a normal relationship between the acid chyme ejected through the pylorus and the neutralizing secretions present in the duodenum.

With slight disturbances of the interrelationship of normal functions in the pyloric region, the ordinary factors active in this segment assume pathologic significance. By experimentally disturbing these relationships, a considerable body of evidence has been developed which stands in answer to Cohnheim's statement that the real difficulty is in determining "the unknown something which prevents the healing of ulcer." The evidence indicates that the "unknown something" may be the normal acid peptic activity of the gastric chyme with the mechanics of the region, which act as a definite handicap once a lesion has been established.

III. AUTOLYSIS OF THE STOMACH

Gastromalacia, or self-digestion of the stomach, is a phenomenon, the occurrence of which during life has been much disputed by pathologists. If the occurrence of autodigestion were possible, one might consider it related to the formation of ulcer so far as one would represent a generalized and the other a localized digestive process. In either case the process could be attributed to an abnormal activity of the digestive enzymes, or to a deficiency of the tissues for natural self-protection against enzymatic activity. That there is such a relationship between autolysis and the formation of ulcer is suggested by the possible occurrence, as reported here, of generalized autolysis of the stomach following surgical drainage of the duodenal juices back into the stomach: the

procedure which resulted in the formation of ulcer. Because of this probable relationship, a brief review of general autolysis and of the resistance of living tissue to gastric digestion is relevant.

The literature contains few references to intra vitam autolysis of the stomach. Its occurrence after death has long been appreciated by pathologists. If an animal is killed at the height of digestion and kept warm, digestion of its stomach and adjacent tissues will take place. Virchow, Elasser and Cohnheim agreed that this was always a cadaverous process. Rokitansky maintained, however, that it occurred during life, particularly in the end-stages of extensive tumors of the brain. Cases reported from Ziemssen's clinic by Mayer and Leube seem to bear out this contention. The mechanism of protection against autolysis has long been a source of speculation and study. Stah believed that the stomach was protected from autolysis by the sensitive soul; John Hunter [128] and Spallanzani believed that the vital power protected the body by some inherent energy. Bernard [129] was the first to view the problem in a physiologic manner, when he attributed this immunity to the fact that pepsin was not absorbed by the gastric mucosa (probably because of the mucous coat), and because any destroyed cells were rapidly regenerated. Harley ascribed the protection to the mucous film, and Pavy to the alkalinity of the blood, which neutralized the acid.

I found only one report of experimental gastric autolysis in the literature. Frouin [130] observed it while studying an isolated stomach with a fistula to the anterior abdominal wall. After transacting the cardia and pylorus, he anastomosed the esophagus and duodenum, so that the continuity of the digestive tract (with the stomach excluded) was reestablished. He closed the two ends of the stomach, and established a fistula to the anterior abdominal wall. Besides this surgical fistula, another smaller one formed accidentally between the cardia of the stomach and the esophagus. Through this fistula small quantities of food seeped into the stomach and were retained. The animal died on the twenty-ninth day, and necropsy was done within two hours. Almost complete digestion of the gastric mucosa had occurred. Frouin believed this resulted from stagnation of the products of protein digestion and gastric secretion. He repeated the study on an isolated stomach, administering salt to increase gastric secretion and injecting peptone into the stomach. Hemorrhage into the stomach resulted, which he assumed

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128. Hunter, quoted by Turck: J. A. M. A. **46**:1753 (June 9) 1906.

129. Bernard, Claude, quoted by Dragstedt and Vaughan: Arch. Surg. **8**:791 (May) 1924.

130. Frouin, Albert: Des causes de la résistance de l'estomac à l'auto-digestion, Compt. rend. Soc. de biol. **52**:749, 1900; Auto-digestion expérimentale de l'estomac, Presse méd. **16**:769, 1908; Resistance de l'estomac à l'auto-digestion, La pathogénie de l'ulcère, ibid., p. 809.

would have resulted in autolysis if repeated often enough. In my study two cases of autolysis followed drainage of the duodenal juices back into the stomach, which caused an unbalanced intermixture of the digestive juices. In analyzing this phenomenon, the causative factors may be attributed to one of two factors: to increased enzymatic activity associated with prolonged retention of digestive juices which results from the procedure, or to deficiency in the normal protective mechanism of the mucosa.

The enzymatic activity of the digestive juices is analogous to the general autolytic or enzymatic activity elsewhere in the body. The analogy is similar to that existing between the endotoxins and ectotoxins of bacteria. Corresponding to endotoxins the tissues contain peptic, tryptic and ereptic-like enzymes which are active within the cell in metabolism, disease, involutional changes and death. Turck,[39] Effront and Robertson showed that these proteolytic intracellular enzymes belong to the same group as the digestive ferments. Analogous to bacterial ectotoxins are the enzymes of the gastro-intestinal tract, active outside the cell body, ordinarily inhibited from attacking the living mucosa, but reported in this paper to have possibly done so.

The first realization that the most constant tendency of tissue is toward spontaneous disintegration came, according to Levene,[131] when Manassein and Buchner [132] demonstrated a single substance in the cell which led to fermentation after the cell was crushed and dead. Salkowski [133] recognized that disintegration of liver, muscle and suprarenal gland was due to enzyme activity, and called the process "autodigestion"; in 1900, Jacobi,[134] introduced the name "autolysis." An appreciation of the universality of this process soon followed. Mueller [36] showed that resolution in pneumonia was by autolysis, and Opie that the exudate was absorbed by the proteolytic activity of leukocytes. That pathologic processes represent only an intensified picture of normal protein metabolism by enzyme activity was first suggested by Dochez.[135] Flexner noted the intense self-digesting tendency in the organs of those who succumbed to typhoid and other infectious diseases. This process also occurs during life, in phosphorous poisoning, acute yellow atrophy, atrophy of the thymus gland, involution of the uterus and softening of tumors. Sykes and Meyers asserted that autolysis is a normal metabolic activity, for during a prolonged fast the amino-acid content of the blood

131. Levene, P. A.: Autolysis, The Harvey Lectures, 1905-1906, p. 73.

132. Manassein and Buchner, quoted by Levene: Autolysis, The Harvey Lectures, 1905-1906.

133. Salkowski, quoted by Dochez: J. Exper. Med. **12**:666, 1910.

134. Jacobi, Y., quoted by Dernby: J. Biol. Chem. **35**:179, 1918.

135. Dochez, A. R.: Intracellular Proteolytic Enzymes of Liver, J. Exper. Med. **12**:666, 1910.

is maintained by autolysis of muscle protein. Notwithstanding the presence of destructive enzymes in all tissues, however, the organs succeed in guarding their integrity, as does the stomach, from enzyme activity. It is only when there is an exaggeration of the normal process, or a disturbance in the normal relationships which keep autolysis within bounds, that self-digestion ensues.

Bile may play a part in this process of gastric autolysis, as indicated by Tatum.[136] He cut blocks of various tissues and incubated them in fresh bile for from two to four hours at 30 C. They were sectioned and stained, and autolysis of the peripheral margins was found, with pyknotic nuclei which had lost their staining capacity for hematoxylin. No such effect was shown in dead tissue subjected to the same process. The action was accelerated by acid, but was inhibited by blood serum and alkali. In an effort to determine the constituent of the bile responsible for this phenomenon, he studied the effect of sodium glycocholate which he found less penetrating than either taurocholate or mucin-free bile, both of which had equal influence in causing the change. Unaltered bile was most penetrating. Boiling did not affect its influence, but animal charcoal diminished it. Bradley and Taylor[137] criticized this work because histologic changes were interpreted in terms of chemical action. They attributed the results to the solvent action of bile salts on the cell lipoids, claiming that the picture was that of cytolysis and not one of enzyme activity.

One of the possible variants that is of major importance in autolysis is the hydrogen ion concentration; this has been recognized as a controlling factor. Hedin,[138] among the earliest investigators, reported increased autolysis in an acid medium and decreased activity in an alkaline medium; he also reported that if the action is started in acid first and then transferred to alkali the autolysis is more complete than if acid acted alone. Morse[139] considered that autolysis is an autocatalytic reaction due to spontaneous increase in the hydrogen ion concentration. Bradley believes that the increase in the hydrogen ion concentration alters the proteins into forms more readily digested by enzyme activity. Dernby[140]

136. Tatum, A. L.: The Influence of Bile on Autolysis, J. Biol. Chem. **27**:243, 1916.

137. Taylor, F. J.: Duodenal Ulcer in the Dog, Vet. J. **78**:343, 1922. Bradley, H. C.: Autolysis and Atrophy, Physiol. Rev. **2**:415, 1922; Studies on Autolysis: VIII. The Nature of the Autolytic Enzymes, J. Biol. Chem. **52**:467, 1922. Bradley, H. C., and Taylor, F. J.: Studies on Autolysis: V. The Influence of Bile on Autolysis, J. Biol. Chem. **29**:281, 1917.

138. Hedin, quoted by Dernby: J. Biol. Chem. **35**:179, 1918.

139. Morse, M.: Enzyme and Reaction of Medium in Autolysis, J. Biol. Chem. **30**:197, 1917.

140. Dernby, K. G.: A Study on Autolysis of Animal Tissues, J. Biol. Chem. **35**:179, 1918.

found three distinct groups of proteolytic enzymes in the tissues, with end-products identical with those of pepsin, trypsin and erepsin of the gastro-intestinal tract, each acting at a different hydrogen ion concentration. In studying different tissues he found the stomach to contain a large amount of pepsin, with optimal activity in a hydrogen ion concentration range of from 2 to 3. This enzyme was present in all tissues, acting at an optimal hydrogen ion concentration of 3.5 and splitting proteins into peptones, but no farther. Trypsin-like and erepsin-like enzymes were present, acting in an optimal hydrogen ion concentration of 7.8, attacking only peptones and peptides, and yielding amino-acids. Self-decomposition of tissue proceeded best at a hydrogen ion concentration of from 5 to 6, that is, between the optimum for pepsin and trypsin. Bradley criticized Dernby for his use of the terms peptic, tryptic and ereptic enzymes, because he claimed these tissue enzymes have a different optimal hydrogen ion concentration than the digestive ferments. He found that tissue protease is inhibited at a hydrogen ion concentration of 2.6, which is optimal for pepsin, and that pepsin is least active at the optimal hydrogen ion concentration for tissue autolysis. He also found that the addition of trypsin carried the splitting of proteins beyond the point to which autolysis alone could carry it.

Another contribution on the influence of hydrogen ion concentration is the work of Rona and Mislowitzner in which they found that autolysis of the liver of guinea-pigs was maximal with acetate buffers of p_H from 3.5 to 3.8, and with phthalate at p_H 4.2. The action was arrested by changing it briefly to p_H 8. Most of the nitrogen in the autolysate was found in the form of polypeptides with 50 per cent autolysis; if the products of digestion were removed by dialysis, the digestion was increased to 90 per cent. Nagai,[141] while studying the pancreatic juice, found that with increased acidity the initial velocity of autolysis was decreased, but that it recovered in a number of hours. He also found that increased alkalinity augmented the initial velocity, but that it soon fell, indicating destruction of the enzyme.

Thus it may be seen that surviving tissue variations in the hydrogen ion concentration can augment the destructive action of proteolytic enzymes. It may be that the abnormal chemical status which the present operative procedure establishes, with fluctuations from acid to alkali, renders the proteolytic enzymes of the digestive tract abnormally active, leading to digestion of the stomach. However, there is another factor that must be considered, that is, the possible impairment of the normal mechanism of protection against the action of these enzymes.

Bernard first demonstrated the power of the digestive juices to disintegrate living tissue by introducing the leg of a frog into a dog's stomach

141. Nagai, Kazuo: On the Autolysis of Pancreatic Juice, J. Biochem. **2**:399, 1922-1923.

through a fistula and watching the digestion of it. Pavy found this to be true also of a rabbit's ear. He believed that in the wall of the stomach the alkalinity of the blood neutralized the hydrochloric acid. Schiff [92] demonstrated that the mucous layer protects the stomach from pepsin by showing that the mucus which forms over the orifice of a canula placed in a gastric fistula will allow the passage of hydrochloric acid, but not of pepsin. De Klug,[142] seeking to verify this protective rôle of mucus, made a powdery extract of intestinal mucosa which had all the characteristics of mucin; it inhibited the action of both pepsin and trypsin even when heated. The same inhibiting effect was demonstrated with mucus from bile, and with pseudomucin from an ovarian cyst. Palier [143] believed that the stomach did not digest itself because the mucus and peristalsis of the tract constantly repelled the digestive juices from the wall.

Weinland attributed this immunity to an antiferment contained in the gastric mucosa. Katzenstein stopped the digestion of spleen and living intestine by adding an extract of gastric mucosa to the gastric juice. Lecine and Hatz found that a fragment of gastric mucosa inhibited the digestion of egg white, which was not true of intestinal mucosa. Kawamura, studying this antiferment, took equal sized pieces of gastric mucosa, intestinal mucosa and spleen and added each to digesting gastric juice according to Katzenstein's conditions. The stomach slightly inhibited digestion, the intestine somewhat more and the spleen most of all. Blood serum also exercised a decided inhibitory effect on digestion. He concluded that there is an antipepsin in the blood, demonstrable in the gastric mucosa and other tissues, and that ulcer arises from a circulatory disturbance resulting in a lack of antipepsin in a circumscribed area of the stomach. All of these observers considered autolysis as due to a break in the equilibrium between enzyme and anti-enzyme, predisposed to by vascular changes and by traumatic and nervous lesions. Lieblin, studying the quantitative value of antipepsin in the blood, found it fairly constant in healthy and sick persons, but in cases of gastric ulcer it was inconstant, sometimes high and sometimes low.

Surgical procedures have been used to study this immunity of living tissue to digestion. Katzenstein introduced a loop in intestine into the stomach of a dog, and death resulted in eight days from digestion of the loop. He obtained the same result with a rat. He then anastomosed a resected segment of intestine at two points on the greater curvature, so that the gastric juice passed through it as a collateral canal. After several days the dog died with necrosis and digestion of the mucosa of

142. De Klug, Ferdinand: Pourquoi les ferments protéolytiques ne digérent-ils pas l'estomac et l'intestin sur le vivant? Arch. internat. d. physiol. **5**:297, 1907.

143. Palier, E.: Etiology of Gastroduodenal Ulcer, New York M. J. **117**:659, 1923.

the implanted segment. The peritoneal surface of a loop of duodenum was implanted into an opening made in the pyloric antrum. This resisted digestion. Implanted spleen and omentum were promptly digested. Katzenstein concluded that the gastric mucosa contained antiferments which were not present in the intestinal mucosa. Lecine and Hatz, on the contrary, found that when great care was taken not to injure the blood supply, the spleen and loops of intestine could be implanted into the stomach without undergoing digestion. They concluded that a tissue which secreted a juice was protected from its action. Stewart suggested that various body membranes have developed a specific resistance to the fluids with which they normally come in contact, but not to other juices. Matthes believed that the gastric mucosa had developed a special resistance to hydrochloric acid, which he claimed was destructive to other tissues.

Dragstedt and Vaughan [70] transplanted flaps of the lower part of the duodenum, and of the upper part of the jejunum, ilieum and colon into the pyloric region with the blood supply intact, and the transplant had not digested at the end of three months. If these patches were sutured with the serosa toward the lumen, the serosa and the muscularis were digested, but the mucosa remained resistant. A split spleen was implanted with its raw surface toward the lumen. It was not digested even though it did not have a mucous coat; also, epithelium grew inward covering its edges. This, it was claimed, ruled out any protective function by the mucous coat, and emphasized the intrinsic resistance of the naked exposed living cell to digestion. Kawamura, using dogs, exposed parts of the stomach, intestinal wall and spleen to the action of gastric juice, but they were not affected while the circulation was unimpaired. Only after necrosis had begun as a result of circulatory disturbance was there any sign of digestion. As mentioned, de Takats and Mann, and later Morton, transplanted jejunal patches into the wall of the stomach. With the exception of one condition, they resisted digestion until after duodenal drainage had been established, which probably resulted in delayed emptying of the chyme and, consequently, prolonged exposure to the acid chyme. Mann also transplanted loops of jejunum into the posterior wall of the stomach. These remained normal until the extirpation of the suprarenal glands, following which autolysis ensued.

METHOD

This study presents two instances of autolysis of the gastric mucosa. The phenomenon was unexpected and was observed after an operative procedure in the study of experimental peptic ulcer.

The operation consisted in draining the duodenal secretions back into the fundic portion of the stomach. The pylorus was severed, and the duodenal end was inverted. The jejunum was severed just distal to the ligament of Treitz.

The distal end was brought up and anastomosed to the open gastric end of the pylorus, thus reestablishing the continuity of the tract, with the duodenum excluded. The distal end of the isolated duodenum was anastomosed to the fundic portion of the stomach, so that the alkaline secretions were drained into that portion of the stomach (fig. 1).

In three of the dogs an effort was made to influence the autolytic process by the administration of different salts contained in capsules. Five grams of sodium chloride was administered to one dog three times a day. This was done because Frouin had administered the salt, and believed that it had increased the tendency to autolysis. To a second dog, 5 Gm. of sodium bicarbonate was given three times a day, on the chance that the process might be initiated by shifting the hydrogen ion concentration, even momentarily, to the alkaline side of neutrality. To a third dog, 5 Gm. of sodium taurocholate was given three times a day with the purpose of augmenting the action of the bile which was completely drained into the fundus of the stomach. Rywosch had produced inflammation and gangrene of the stomach of rabbits by feeding an excess of bile salts. The administration of the salts was continued over a period of a month, but in none of the three dogs did autolysis of the gastric mucosa develop.

RESULTS

Two of twenty-six dogs subjected to the foregoing operative procedure died suddenly. Necropsy revealed extensive autolysis of the gastric mucosa. The first dog died twenty-three days after operation, during which period it had lost 1.8 Kg. At necropsy, both lungs were collapsed and the pleural cavities contained a considerable amount of thin chocolate-colored fluid which was strongly acid. The mediastinum had been entirely eaten away, except for the main blood vessels, the trachea and the lower part of the esophagus. The upper and intrathoracic portions of the esophagus had been entirely eaten away. This explained the fluid in the chest, which, being strongly acid, was probably gastric juice. The digestion had extended through the structures of the neck, and the upper limit was determined by the lower part of the skull. The whole hand could be inserted into the cavity in the neck. The peritoneum was clean and relatively free from adhesions. The stomach had undergone considerable digestion at the points adjacent to the stoma and to the delivery of the duodenal contents. The digestion had entirely destroyed the mucosa, leaving the submucosal vessels standing by themselves. The stomach contained coffee ground material. All anastomoses were satisfactory.

The second dog died five months after operation; it lost 1 Kg. Necropsy revealed autolysis of the stomach and jejunum, and ulcer formation. The peritoneum was clean, and all suture lines were intact. The walls of the stomach appeared thin and transparent as the organ was washed with water. When opened, extensive autolysis of the gastric mucosa was found. Over an area approximately 10 by 7 cm., the cardia was denuded of mucosa, and the glistening submucosa formed the inner lining of the stomach. An area of jejunum close to the anastomosis,

about 2 cm. in width and extending about 5 cm. in a longitudinal direction, was likewise denuded of mucosa. In the center of this autolyzed area, two perforated ulcers were found (fig. 16). The relationship of the autolyzed surface and the ulcers suggested a possible identity between the mechanism that leads to a localized area of destruction, as an ulcer, and that which leads to extensive autolysis of the gastric mucosa.

COMMENT

It is impossible to estimate the significance of the results. They are isolated phenomena in an uncontrolled experiment. It is not possible to judge how much of the process is intra vitam and how much is post-mortem change. It is significant, however, that autolysis occurred in

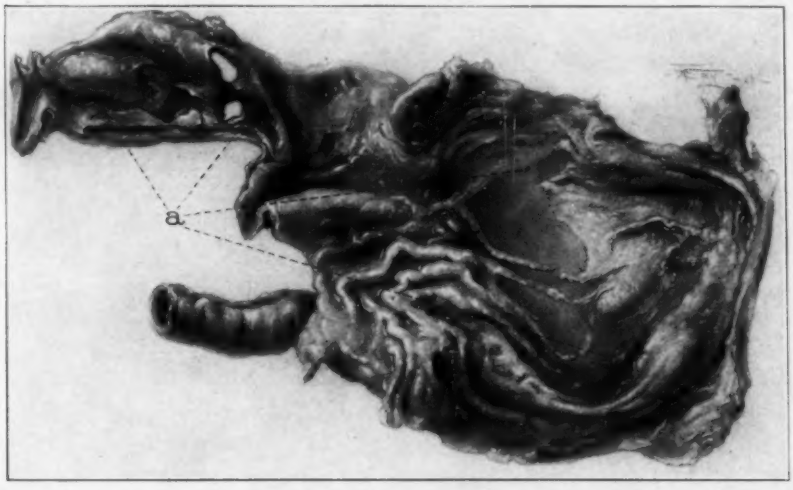

Fig. 16.—Extensive area of autolysis of the mucosa, *a*, of the stomach and jejunum, associated with the formation of perforated ulcers, in an experimental study in which the duodenal alkalis were drained back into the fundic portion of the stomach.

two animals subjected to the same operative procedure, and that they were isolated specimens in a large group of normal and experimental animals all receiving the same kennel care. Shortly after death, all animals were placed in refrigeration. Routine careful investigation of all organs was carried out, and never was this phenomenon observed. It seems fair to assume that the operative procedure established conditions that were conducive to the initiation of the autolytic process.

Conclusions cannot be drawn concerning the relationship of this process to that of general tissue autolysis. In both instances comparable enzymas are active, in the one instance within the cell and in the other instance outside the cell. General autolysis is definitely influenced by

shifts in the hydrogen ion concentration of the environment, and in these instances of autolysis of the mucosa of the stomach there is the possibility of a widely shifting hydrogen ion concentration. It is interesting to speculate whether the conditions of the experiment made it possible for the intragastric enzymes to attack the gastric mucosa. If this is true, it is possible that an ulcer may represent a similar process limited to an area of lowered resistance.

Why does not the stomach digest itself ordinarily? What is the source of protection against this destructive process? This seems to be a problem more open to theory than to exact investigation. In a series of studies which I made on the control of the acidity of the gastric juice, it seemed that in the active state of digestion food combined readily with the acid, and that after the completion of digestion the residual free acid was emptied from the stomach. It appeared that in the resting state the rate of secretion was lowered to a level at which, according to Foster's evidence, it may be combined with the mucus in the presence of pepsin at body temperature. This reaction may take place immediately in the lumina of the glands in the fundus. The gastric mucosa would probably be protected from any residual free acid in the lumen of the stomach by a coating of this mucus capable of combining with the acid.

* * *

SUMMARY OF STUDY III

The literature contains little on autolysis of the stomach. Two such instances, observed in an experimental study, are reported. There may be a general analogy between intracellular enzymatic activity responsible for general autolysis and the extracellular enzymatic activity responsible for the instances of autolysis of the gastric mucosa. This process may represent the mechanism by which isolated ulcers of the mucosa are established, when there is local reduction in the immunity of the mucosa to this autolytic activity. It is probable that the mucous secretion of the stomach by virtue of its capacity to combine with free acid forms the principal defense of the gastric mucosa against autolysis.

LOOSE CARTILAGE FROM INTERVERTEBRAL DISK SIMULATING TUMOR OF THE SPINAL CORD*

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The two loose cartilages here reported were disclosed at operation for presumed tumors of the cauda equina. In each instance the spinal canal was completely blocked as shown by the shadows of iodized oil 40 per cent (figs. 1 and 2). The signs and symptoms were so rapidly progressive and the pain in the spinal column so severe that presumptive diagnoses of carcinoma of the vertebra were made. The fact that the two cases appeared only a few months apart leads me to believe that the lesion may not be so infrequent, although a review of the literature has failed to disclose other cases of their kind. The lesion is a completely detached fragment of cartilage from an intervertebral (lumbar) disk and is surrounded by serum. It bulges dorsally into the spinal canal as a tumor, and by compressing the roots of the cauda equina causes motor and sensory paralysis, loss of reflexes and of rectal and vesical control. The lesion is undoubtedly of traumatic origin.

REPORT OF CASES

CASE 1.—A sparsely nourished man, aged 47, was referred by Dr. Lewellys F. Barker. Whether or not the past history was relevant to the present illness was not clear at the time. Three years earlier a tumor had been removed from the hand; a microscopic diagnosis of a sarcoma was made. The scar on the hand, the regions of the epitrochlear and axillary glands, had since been treated intensively with radium. Subsequently an axillary gland was removed, but no sign of malignancy was discovered. Two years later, he consulted Dr. Barker because of convulsions which dated back two years.

The patient was readmitted to Dr. Barker's service on May 15, 1928, with an entirely different complaint. Ten weeks before admission he had a severe attack of pain in the lumbar region and both hips; there was more pain in the right hip. The pain radiated down the back of both legs, with more pain in the right leg. After two months of excruciating pain, it was necessary to resort to morphine for relief. Six weeks before admission to the hospital, a "dead feeling" developed in both legs and gradually increased. Two weeks before, he was barely able to stand alone. Assistance was necessary to walk a short distance. One week before, retention of urine and feces developed; after that time he was catheterized twice daily. He lost 42 pounds (19.1 Kg.) in weight, 15 pounds (6.8 Kg.) of which were lost in the last two months before admission. Pain in the lumbar region, hips and legs steadily became more severe.

On admission to the Johns Hopkins Hospital, the patient was found to have a total flaccid paralysis below the knees. Except for feeble flexion and extension

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* From the Johns Hopkins University and Hospital.

of both legs at the hips, the legs were useless. Sensation was impaired though not entirely lost; sharp and dull stimulation were not differentiated. Vibratory sense was lost. Flexion and extension of the toes could not be differentiated, though the patient could tell which toe was touched. There was loss of sphincter control of feces and urine (retention of urine was complete). Marked tenderness, even to light pressure, was noted over the spine of the third and fourth lumbar vertebrae. The lumbar muscles were in continuous strong spasm. Movements of the spine were painful, and even coughing intensified the pain. The patient was averse to any movement, and flexion of the knee was painful.

Fig. 1 (case 1).—Shadow of iodized oil at the upper margin of the tumor caused by a loose cartilage of the intervertebral disk.

The abdominal reflexes were normal; the cremasteric reflexes were not obtained, and the knee jerks were subnormal. The Achilles jerks were not obtained, and there was no ankle clonus. The Babinski, Gordon and Oppenheim tests were negative. The Wassermann reaction of the blood was negative. Roentgenograms of the lumbar spine were negative.

Through a cisternal puncture, 0.5 cc. of iodized oil was injected. It stopped abruptly at the level of the third lumbar vertebra.

Preoperative Impression.—The rapidly progressive paralysis, sensory, motor and sphincter, the severe pain and tenderness in the back, the great loss of weight and finally the history of a malignant lesion of the hand (doubtless incorrect) led

me to suspect a metastatic lesion of the third lumbar vertebra, despite the absence of signs of destruction in the roentgenogram.

Operation.—It was decided to explore the lesion to be sure of its character, and if it was malignant to perform a chordotomy. The laminae of the third and fourth lumbar vertebrae were removed. No change in the amount of extradural fat was observed. When the dura was opened, the roots of the cauda equina herniated markedly (fig. 3). The nerves were greatly injected, and because of this increased vascularity, oozing followed when they were touched. It was seen

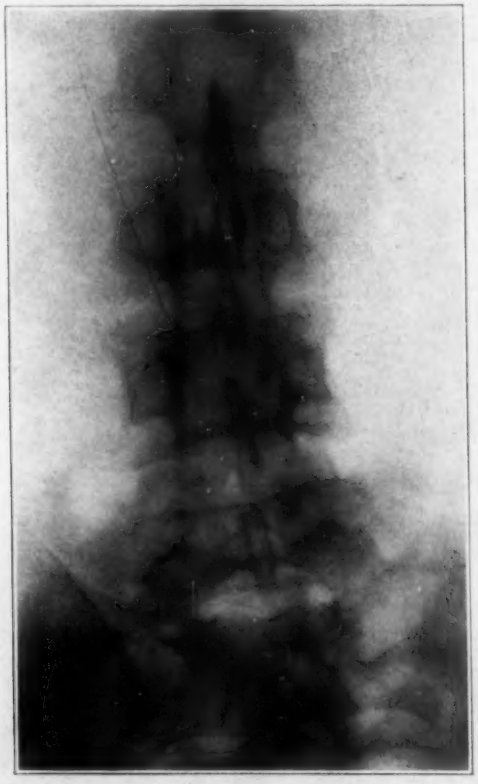

Fig. 2 (case 2).—Iodized oil shadow at the upper margin of the tumor.

that there was a sharp knuckle of the roots protruding backward. Above and below this knuckle, there was a sharp drop. Palpation revealed a hard tumor lying beneath the roots and pushing them through the dural opening. The roots were then retracted to the left, and a bulging tumor mass was seen. It was round, about as large as a big hazelnut (about 1.5 by 1.5 cm.) and entirely covered by dura. It seemed semifluctuant when touched with the point of the forceps. The lesion was still thought to be malignant, even though the ventral dura was intact. After some hesitation I thought it advisable to incise the dura, and much to my surprise a border of loose cartilage protruded through the opening (fig. 4). With forceps, the cartilage was picked up and delivered without resistance. It was roughly oval, but crumpled. When straightened, it measured 2 by 0.8 by 0.3 cm. Its edges

Fig. 3.—Drawing showing the roots of the cauda equina bulging backward.

Fig. 4.—Cauda equina retracted exposing tumor on ventral surface of the canal. The tumor has been incised and the loose cartilage is being delivered.

were very irregular, almost serrated (fig. 5). It had no attachments to the vertebral cartilage. Exploration of the cavity with a small curet revealed no additional sequestrums either of cartilage or of bone. A few drops of fluid escaped with the "floating cartilage." On gross inspection, there was no evidence of bone.

Microscopic Report.—A few scattered cartilage cells in varying states of degeneration were scattered through a pink-staining hyaline mass which was not entirely homogeneous, but in places was broken up by scattered fibrils longitudinally arranged. There were no inflammatory changes. No round or polymorphonuclear cells appeared in the sections, and there were no bone cells or deposits of calcium.

Postoperative Course.—Recovery from the operation was uneventful. The pain, though immediately relieved, was not at once abolished. Gradually it became less and less, and in a few weeks ceased. Vesical control was regained in two weeks and rectal control four weeks after operation. Return of motor power began seven weeks after the operation (three weeks after leaving the hospital). In a letter written six months after the operation, the patient stated that he could walk long distances without support, and every week improvement continued.

Fig. 5.—Loose cartilage removed from patient in case 1.

Subsequent History.—After the nature of the lesion was known, the recent history was again reviewed for trauma. The patient then recalled a severe, sharp lumbar pain which came with a sudden jolt when he was riding horseback three months before, or about two or three weeks before the onset of his present illness. He had forgotten the pain, since it disappeared after a few hours and had not returned during the succeeding days.

CASE 2.—A large, robust man, aged 61, was referred by Dr. Eugene V. Parsonnet of Newark, N. J., because of paralysis of the lower limbs. He had been in perfect health until twelve weeks before, when he pushed his automobile out of the driveway. Immediately afterward, a dull, heavy pain developed in the small of the back. He went about his duties, and in a few days the pain abated. A week later, without appreciable cause, a sudden excruciating pain struck the lumbar region and radiated down the posterior aspect of both thighs. The pain was so severe that he had to remain in bed for two or three days. Movement of the spine caused severe pains. A few days later, he was again relieved, and returned to work. Ten days after the second attack, he was seized with a third and even more severe pain at the same site and with the same referred distribution.

At this time (about a month after the first pain), he was seen by Dr. Parsonnet, who noted the following: 1. The normal anterior lumbar curve was missing.

2. There were definite scoliosis of the lumbar spine to the right. 3. Marked spasm of the erector spinae muscles. 4. Moderate tenderness at the third and fourth lumbar spinous processes. 5. The right knee jerk was diminished and the right ankle jerk absent. The patient was able to stand, but any movement elicited great pain.

An orthopedic consultant was called who advised stretching the sciatic nerves. This was done under deep anesthesia with ether. A plaster jacket was applied with the back in hyperextension. The spica extended to the toes of the right foot; the left leg was left free. On recovery from the anesthesia the patient was unable to void, but this was considered a sequel of the anesthesia. Three days after application of the cast, loss of power developed in both feet; he was unable to flex the toes. A slight edema of the left ankle (not included in the cast) developed.

Fig. 6.—Remains of cartilage cells. There are no evidences of inflammation.

Two days later (five days after the cast had been applied), he could not move his left leg (the right was in the cast) and there was incontinence of feces. On the following day, the cast was removed.

A neurologist who was called in consultation noted the following: 1. There was loss of deep and superficial sensation from the toes to the hips and loss of sensation around the anus. 2. The patient was unable to make any movements of either foot or leg below the knee. He could flex and extend the leg at the hip. This was some improvement, for two days earlier he was reported to be unable to make any movement of the leg. Paralysis was of the flaccid type. 3. Examination of the reflexes showed the ankle and right knee reflexes absent, the left knee reflex was diminished, and the abdominal and cremasteric reflexes were normal. 4. There was loss of vesical and rectal control. 5. Tenderness persisted over the third and fourth lumbar vertebrae. A lumbar puncture was done; the fluid was clear and colorless and registered 10 mm. of pressure with the mercurial manometer; jugular compression (Queckenstedt test) caused the pressure to rise instantly

to 30 mm., and on release of jugular pressure, the fluid promptly fell to the former level. The cell count was normal and there was no increase of globulin.

The patient was referred to me twelve weeks after the strain in the back and three weeks after the sciatic nerves had been stretched and the cast applied. The physical and neurologic observations were essentially the same as those just reported: 1. Sensation of every form was absent below the third lumbar segment but it was normal above this segmental level. 2. Flexion, adduction and extension of the leg at the hips were possible but decidedly weak while abduction was absent; there was no movement at the knee, ankle and toes. 3. All reflexes were abolished at and below the knee. 4. There was complete loss of vesical and rectal control. Lumbar puncture showed definite xanthochromia, the fluid having a greenish-yellow tint. The cell count was 10. The Queckenstedt test was negative, the column of fluid rising and falling with application and release of jugular compression. Iodized oil was injected; it descended only the distance of half a vertebra, lodging at the level of the fourth lumbar vertebra (fig. 2).

The only abnormality that could be detected in the roentgenograms (anteroposterior view only) was a supernumerary lumbar vertebra. The intervertebral disks appeared normal in size and shape.

Preoperative Impression.—That a tumor completely blocking the spinal canal was present at the level of the third lumbar vertebra seemed certain. That there was a definite relationship to the "stretching" of the sciatic nerves because of the sensory, motor and sphincter loss that occurred promptly thereafter could hardly be questioned. But it was necessary to admit that there was a preexisting lesion which had caused the severe pain in the back and down the legs. Though a metastatic lesion of the vertebra was suspected, no destruction of bone could be seen in the roentgenogram and no primary carcinoma could be found, though carefully sought. The true nature of the lesion was not suspected.

Operation.—Laminae of the fourth and fifth lumbar vertebrae (corresponding to the normal third and fourth) were removed under rectal ether anesthesia. Before the dura was opened, one could feel a hard mass about 1.5 cm. long, but when it was opened no tumor was visible. The roots of the cauda equina covered the exposed field. However, a sharply defined hillock of the cauda equina pushed backward, and under it one could still feel tumor of bony hardness. The roots of the cauda equina were definitely reddened and swollen. The cauda equina was retracted from the right side with a blunt dissector and a well circumscribed bulging extradural mass was at once visible; it crossed the midline posteriorly but was more on the right than the left. The mass was white, being covered with intact dura. When pressed firmly with the end of the forceps it seemed to fluctuate; at least it was soft in the center where it gave evidence of pointing. At once the picture of case 1 was recalled to mind for the gross appearance of the swelling was the same in both cases. The dura was slit longitudinally for a distance of about 1 cm. It was entirely avascular. A piece of loose cartilage projecting into the dural opening was picked up with the forceps and easily delivered (fig. 7). It was entirely unattached and no force was required to withdraw it. A few drops of fluid escaped with the floating cartilage. Further exploration of the cavity was not attempted. The borders of the cartilage were irregular; there was no sign of infection, no redness of the cartilage and no redness of the dura which covered the tumor. No fragments of bone were found attached to the cartilage. The cut edges of the dura sank back into the cavity from which the cartilage was removed. The knoll of the cauda equina entirely disappeared. The alinement of the vertebrae was normal.

Microscopic Report.—Exactly the same microscopic picture presented as in the preceding case. A few scattered cuts of cartilage were present, though in varying degrees of preservation. There was no cellular reaction indicative of an inflammation.

Subsequent Note.—The patient's recovery from the operation was uneventful. Urinary control returned ten days, and rectal control one month, after operation. Some sensation had returned within a month. He was beginning to walk four months after operation. Doubt of eventual complete recovery of motor function as in case 1 can scarcely be entertained, for the nerves are intact and apparently uninjured.

ANALYSIS OF CASES

In each case a large fragment of the intervertebral cartilage had become detached and was acting as a sequestrum. The reaction to the "foreign body" caused a swelling which bulged dorsally into the spinal canal (fig. 8). Pressure on the roots of the cauda equina then produced paralysis of all function below the nerve level of the tumor and through edema some function was lost for distance above the tumor.

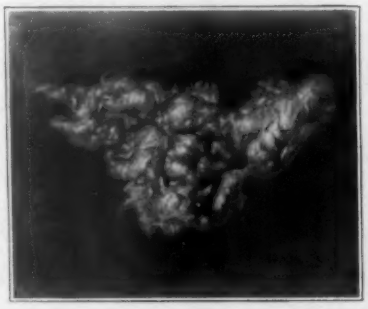

Fig. 7.—Loose cartilage removed from patient in case 2.

The detached cartilage is almost certainly the result of trauma, but a relatively trivial trauma. In the first case no history of trauma was given voluntarily; it was elicited only after trauma was suspected. The trauma in the second case was almost surely the slight wrench caused by pushing an automobile. Several attacks of pain identical in both character and location were again induced by slight trauma before the advent of paralysis, and the location of the pain remained the same after the paralysis developed. The severe trauma incident to "stretching the sciatic nerves" and to placing the body in the cast with the lumbar region flexed undoubtedly caused the lesion to fulminate and promptly to reach the stage of tumor formation some time in advance of the normal course of events.

The preoperative diagnosis of a lesion in the vertebra could hardly be questioned in either case, because the slightest movement of the lower part of the spine always brought on or intensified the pain. Moreover, the tense spasm of the erector spinae muscles and the sharply

localized severe tenderness of the spinous process offered supporting evidence of the strongest kind. In these respects the lesion is hardly different from carcinoma of the vertebra. In either condition, only the recumbent posture could long be tolerated.

In both patients, the pain radiated down the back of both legs but usually down one more than the other. The side most involved proved to be the side of the greater bulge of the tumor. These facts lead one to wonder whether bilateral sciatic pains do not in most instances indicate a lesion affecting the spinal cord or cauda equina, more frequently

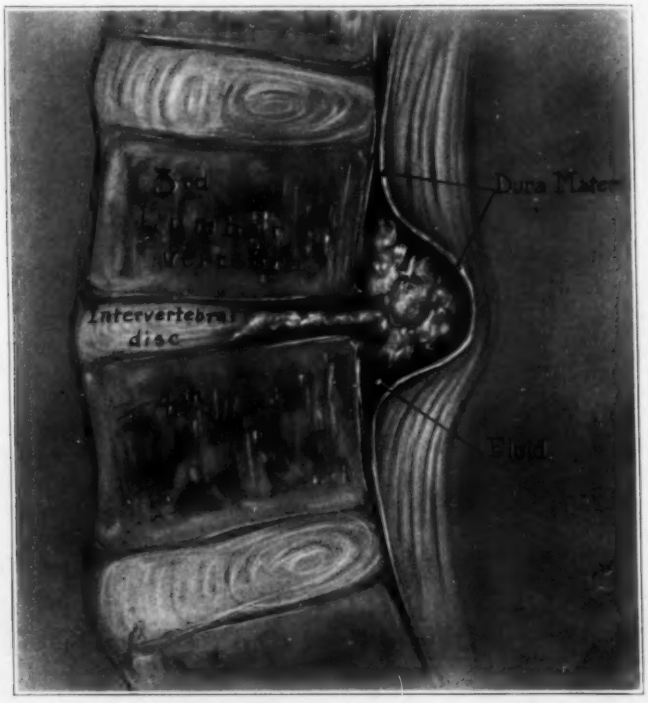

Fig. 8.—Sketch to show conception of position and manner of formation of loose cartilage projecting into the spinal canal and compressing the cauda equina.

the latter. These cases at least offer pathologic evidence of a definite lesion inducing symptoms of so-called sciatica with its all too meager pathology.

That the floating cartilage in each of these cases was in the lumbar region is doubtless significant. The maximum effects of shocks and of torsion of the body are transferred to the lumbar spine. As protection against shocks, the intervertebral disks attain their greatest size in the lumbar region. That the lesion occurs about the middle of the lumbar spine is probably also because of an additional point of least

resistance, for here the maximum part of the anterior lumbar curve is attained. Certainly movable vertebrae on a curve offer the maximum opportunity for localized effects of trauma.

That the lesion occurs on the posterior instead of on the anterior aspect of the lumbar vertebra is probably also significant. The normal anterior curvature of the lumbar spine would be expected to throw greater localized effects of trauma on the posterior side of the disk. In other words, the cartilage should be more readily pinched posteriorly than anteriorly. Then, too, the relatively thin and incomplete posterior ligaments of the lumbar spine should more readily permit protrusion of a tumor in the intervertebral disk than the stronger and complete anterior ligament. Whether a loose cartilage could push through the strong and firmly attached anterior ligament can only be conjectured. There is as yet no evidence that a loose cartilage forms only in the posterior part of the disk though it may well be possible. From the size of the extended cartilage as seen at operation, it is hardly possible that more than a third or at most a half of the anteroposterior diameter of the disk can be involved.

Finally, in both instances the tumor presented not in the midline but to one side. Doubtless the explanation for this fact is that the posterior common ligament is defective laterally along the lumbar spine. Since the lesion is of traumatic origin it is probably not without significance that both of these patients are men. It is also not improbable that the additional lumbar vertebra in one patient may have had some part in making the lumbar spine susceptible to injury.

Emphasis has been placed on the seemingly trivial injuries that cause the cartilaginous sequestrum formation. It is not improbable that the repetition of minor traumas may, at times, at least, be an important factor. The history of the repeated attacks in case 2 suggests this possibility. There must be many instances in which the intervertebral cartilage sustains the degree and character of injury experienced in these two cases, and yet subsequently heals instead of going on to sequestration. It is difficult to believe that the complete detachment of the cartilaginous fragment does not require considerable time, and that with proper rest and fixation of the spine this outcome may be avoided. A remarkable contrast in the disposition of fragments of intervertebral cartilage is presented by severe fracture dislocations of the spine. There the cartilage is badly torn and frequently fragmented, but in the process of healing it is organized with bone and fibrous tissue into a solid mass.

The x-ray has disclosed nothing in either of these cases. After the character of the lesion was known, the roentgenograms were again inspected, with negative results. However, only anteroposterior views were taken before operation, and positive signs would hardly be expected from this view. However, shortly after operation on the

second patient, lateral stereoscopic views of the affected part of the spine were taken, and not the slightest defect could be seen. The absence of bone in the sequestrum might well preclude the delineation of the tumor.

DIAGNOSIS

It is not difficult to arrive at the diagnosis of a tumor of the cauda equina because of the progressive paralysis—sensory, motor and sphincter—and loss of reflexes. The rapid progression of these signs and the severe pain in the back, the rigid lumbar spine due to spasm of the erector spinae muscles and the marked tenderness over the spinus processes and laminae of the lumbar vertebrae are such as to make metastatic carcinoma of the body of the vertebra the most likely diagnosis. The absence of roentgenologic changes in the body of the vertebra would appear to carry much importance in the differential diagnosis between this lesion and metastatic carcinoma or sarcoma of the body of the vertebra. The malignant lesions are almost the only ones that offer difficulties in differential diagnosis.

Aside from the negative roentgen changes in the body of a vertebra, there seems to be no absolute differential objective evidence. Even the clinical and microscopic examinations of the cerebrospinal fluid may show no differences, for both lesions are extradural. Each may give a mild degree of xanthochromia and globulin increase. Both give a negative reaction to the Queckenstedt test if the block is caudal to the point of entry of the needle, and both show a complete block at the upper level of the tumor when iodized oil is injected.

In the differential diagnosis two considerations are all-important: (1) to make the clinical diagnosis of carcinoma only on absolute evidence, i. e., microscopic or roentgenologic, and (2) to accept the operative diagnosis of a malignant condition only on positive evidence. My willingness to accept suggestive evidence of malignancy nearly deprived the first patient of the opportunity of having the lesion explored. In fact, had he not been eager to grasp the faint hope which an operation offered, the lesion would not have been disclosed. Even at operation the bulging mass from the body of the vertebra was at first considered so surely malignant that there seemed little reason to open the tumor.

The order of return of the various functions is most interesting. In both cases the vesical control returned completely in about ten days. Rectal control returned in about one month in each instance. Sensation gradually returned in about a month, but motor power made no improvement whatever until from seven to eight weeks after the operation in the first case, and at the end of the second month the motor power had not yet returned in the second patient. In the first case the motor improvement came slowly and continued for several months.

RESEMBLANCE OF THIS LESION TO OSTEOCHONDRITIS DISSECANS OR TRAUMATIC JOINT-MICE

Superficially at least, the loose vertebral cartilage appears to resemble the loose cartilage of the knee, elbow and ankle joint following osteochondritis dissecans described by König in 1888. They differ in that fragments of bone were not attached to the cartilage in either of my cases. The environment too is greatly different in that there is no cavity—even potential—as in the knee and elbow joints. More common in the knee joint than elsewhere, this condition has come to be recognized as a clinical entity, but the dividing line between osteochondritis dissecans and other joint-mice appears to be none too sharp. The distinction is usually made that in osteochondritis dissecans the loose bodies occur singly or at most in pairs, and that there is no evidence of inflammatory joint involvement elsewhere. König [1] could find no evidence of traumatic or constitutional origin and for that reason considered them to represent a distinct pathologic process. Barth [2] thought they were purely of traumatic origin. Ludloff, who first diagnosed them by roentgenograms and treated them surgically, thought that they were due to occlusions of end-arteries. Other authors (Freiberg and Wooley,[3] Ridlon,[4] Codman,[5] Weil,[6] Anglin [7] and Troell [8]) have come to no more definite conclusion. Büdinger [9] (1907), Axhausen [10] (1914), Kappis [11] (1920) and Brackett and Hall [12] (1917) were more positive of their purely traumatic origin. They also called attention

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1. König: Ueber freie Körper in den Gelenken, Deutsche Ztschr. f. Chir. **27**:90, 1888.

2. Barth: Die Entstehung und das Wachstum der freien Gelenk-Körper, Arch. f. klin. Chir. **56**:507, 1898.

3. Freiberg and Wooley: Osteochondritis Dissecans, Am. J. Orthop. Surg. **8**:477, 1910.

4. Ridlon: Osteochondritis Dissecans, J. A. M. A. **61**:1777 (Nov. 15) 1913.

5. Codman, E. A.: Formation of Loose Cartilages in the Knee Joint, Boston M. & S. J. **149**:427, 1903.

6. Weil, S.: Ueber doppelseitige symmetrische Osteochondritis dissecans, Beitr. z. klin. Chir. **78**:403, 1912; Ztschr. f. Chir. u. Mech. Orth., July, 1912.

7. Anglin, R. H.: Loose Bodies in the Knee, with Special Reference to Their Etiology and Growth, Brit. J. Surg. **1**:650 (April) 1914.

8. Troell, A.: The Origin of Free Bodies in the Knee with Special Reference to Osteochondritis Dissecans, Arch. f. klin. Chir. **105**:399, 1914.

9. Büdinger: Ueber traumatische Knorpelrisse im Kniegelenk, Deutsches Ztschr. f. Chir. **92**:510, 1907.

10. Axhausen: Die Entstehung der freien Gelenk-Körper und ihre Beziehungen zur Arthritis deformans, Arch. f. klin. Chir. **104**:581, 1914.

11. Kappis: Osteochondritis dissecans und traumatische Gelenkmäuse, Deutsche Ztschr. f. Chir. **157**:187, 1920.

12. Brackett, E. G., and Hall, C. L.: Osteochondritis Dissecans, Am. J. Orthop. Surg. **15**:79, 1917.

to the fact that the injury may be slight and repeated. The present trend of opinion seems to be that the term osteochondritis dissecans is a misnomer (for there is no evidence of inflammatory character), and that it is better to classify these loose bodies under traumatic joint-mice.

SUMMARY

1. Following slight (or repeated) trauma a fragment of an intervertebral disk may become detached, and eventually bulge into the spinal canal as a tumor. The "tumor" is composed of the cartilage and fluid formed by reaction to the foreign body.

2. Two instances of this lesion are reported, both being disclosed at operation. Both are in the midlumbar region, and both occurred in men during the latter half of life.

3. The trauma at onset is relatively trivial and perhaps repeated. The lesion is probably similar to osteochondritis dissecans or traumatic joint-mice of the elbow and knee joint.

4. The early symptoms are those of localized vertebral pain plus bilateral sciatica—one side being affected more than the other. Later, the symptoms are rapidly increasing paralysis, sensory and motor paralysis and loss of urinary and vesical control and of reflexes—all due to compression of the cauda equina.

5. The signs and symptoms suggest carcinoma of the vertebra. This preoperative diagnosis was made in both cases.

6. This lesion offers a pathologic basis for cases of "so-called sciatica," especially bilateral sciatica.

7. The lesion is cured by operative removal of the cartilage.

RENAL COUNTERBALANCE *

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The theory of renal counterbalance was introduced by Hinman [1] in 1922. Before this article appeared, little, if anything, had been written concerning the possibility of renal atrophy of disuse, and according to Hinman this type of renal atrophy was a new conception, even though a similar process had long been recognized in other organs, such as muscle and bone. It is remarkable that a conclusion had not been crystallized concerning atrophy of disuse when applied to the kidney. Indeed, the subject seems to have been unnoticed until Hinman applied it as the basis for his theory of renal counterbalance.

According to this theory, a kidney, after sustaining a temporary injury, as, for example, a temporary period of ureteral obstruction causing hydronephrosis, will go on to complete or almost complete atrophy if allowed to function in competition with its hypertrophic mate. Thus, if the ureter of a kidney is obstructed for two or three weeks, this kidney becomes hydronephrotic and its mate undergoes hypertrophy. If at the end of this time the obstruction to the ureter is relieved, the hydronephrotic kidney supposedly will be placed at a distinct disadvantage. According to the theory of renal counterbalance, the kidneys enter into functional competition and the weaker kidney eventually goes on to complete or almost complete atrophy. In the words of Hinman:

> "The healthier side will gradually undergo a compensatory hypertrophy which may be so capable of counterbalance as to render the work of its weak assistant unnecessary, disuse atrophy of which will progressively occur. The reapportionment of functional activity after the alteration occurs by a competitive type of anatomic compensation."

He also stated:

> "An animal cannot live after opposite nephrectomy, with a repair hydronephrosis of longer than from two to three weeks. Any repair hydronephrosis, even of

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1. Hinman, F.: Renal Counterbalance: An Experimental and Clinical Study with Reference to the Significance of Disuse Atrophy, Tr. Am. Ass. Genito-Urin. Surg. **15**:241, 1922; Renal Counterbalance, Arch. Surg. **12**:1105 (June) 1926.

two weeks, will usually eventuate in complete atrophy if the opposite kidney remains healthy and undisturbed. . . ."

The experiments quoted by Hinman on which this theory is based, although numerous and variegated, are somewhat inconclusive. The following two experiments are taken from Hinman's monograph and seem to have the most direct bearing on the subject. The author stated that he has carried out similar experiments, but unfortunately they were not completely reported in his publication.

"Experiment 5.—Late atrophy of hydronephrotic repair; ureteral obstruction of twenty-one days; repair period of 249 days.

"Dog 5, weighing 20 pounds (9 Kg.).

"There was a complete obstruction of the left ureter for twenty-one days. After a ureterocystoneostomy, and a drainage period of 249 days, the urine was free from bacteria and pus. The dog was killed, under ether, with preliminary functional study. The appearance time of phenolsulphonphthalein was four minutes for the right kidney, and eight minutes for the left. In the first fifteen minutes, 25 per cent of the dye was excreted by the right kidney, and 5 per cent by the left; in the second fifteen minutes, 20 per cent by the right kidney and 2.5 per cent by the left, the total excretion for the first half-hour being 45 per cent for the right kidney and 7.5 per cent for the left. At necropsy, the left kidney weighed 15 Gm.; the right, 48 Gm. The ureter was freely patent. There was no pelvic dilatation on section and no evidence of infection. [An illustration] shows that the left kidney was reduced to one third its size, and that, even in the gross, cortical atrophy was quite marked."

"Experiment 8.—Thirty days left hydronephrosis; left ureterocystoneostomy; seven days later, partial obstruction of right ureter. Killed in 390 days.

"Dog 8, a male shepherd, weighing 42 pounds (19.1 Kg.).

"Nov. 1, 1920, ligation of left ureter.

"Blood urea nitrogen, 18 mg. per hundred cubic centimeters; nonprotein nitrogen, 34 mg. per hundred cubic centimeters; phenolsulphonphthalein, 70 per cent in two hours. . . .

"December 2, left ureterocystoneostomy.

"December 9, partial ligation of right ureter. Under ether anesthesia and surgical asepsis, the abdomen was opened in the midline just below the umbilicus.

". . . The right ureter was identified in its bed as low down as possible without disturbing the recent operative area behind the bladder. A short length of ureter was freed in an area about 3 cm. from its point of entry into the bladder, and a rubber band 2 mm. wide was placed around it and stretched. The ends of the band thus stretched were tied with silk so as to form a moderate constriction of the ureter. . . . The animal recovered slowly from the operation. . . . A month after operation, he seemed quite normal and ate normal amounts.

"Nov. 29, 1921, . . . urea nitrogen, 26 mg. per hundred cubic centimeters; nonprotein nitrogen, 49 mg. per hundred cubic centimeters, and creatinine, 1.93 mg. per hundred cubic centimeters.

"Jan. 4, 1922, killed. Necropsy: The dog was in excellent condition; the weight was 42.5 pounds (19.3 Kg.). . . . The animal had been passing well formed stools and clear urine. Phenolsulphonphthalein, the first hour, was 53 per cent;

the second hour, 20 per cent. Blood urea nitrogen was 21 mg. per hundred cubic centimeters; nonprotein nitrogen, 41 mg. per hundred cubic centimeters. The dog was killed with ether.

" . . . The abdominal organs, except for the genito-urinary tract, presented no lesions whatever. The heart was not enlarged and showed no pathologic alterations. The lungs were clear. A sample of urine from the right ureter was clear and showed a considerable amount of pigment. The urine from the left ureter was cloudy. It showed an equal amount of pigment. . . .

"The left kidney was normal in shape and slightly enlarged. It collapsed readily at the hilum with pressure, showing a slight degree of hydronephrosis. The ureter of the kidney was very large, being 1 cm. in diameter. It was not tortuous. Its opening lay in the midline of the bladder posteriorly and was fully patent. . . . The right kidney was very large and had a very thin wall. There was a crescentic nodule of parenchyma at its upper pole 1½ cm. thick and 7 cm. long. In all other areas, the wall was of paper thinness. The ureter was slightly larger than that of the opposite side. It was 1.3 cm. in diameter. It was much thinner than the left ureter and very tortuous. Near the bladder, it presented an obstructed area, at which point the rubber band, placed Dec. 9, 1920, was localized. Beyond this, it was of normal diameter. The right ureterovesical orifice through which this ureter opened was normal in all respects. . . . Gentle pressure on the hydronephrotic sac caused a flow of fluid through this ureteral orifice. The wall of the bladder was normal in appearance. . . . The respective sizes and weights of the two kidneys were as follows:

	Length (Pole to Pole)	Width (Side to Side)	Depth (Hilum to Greater Curve)	Weight	Pelvic Capacity
Left kidney....	6.95 cm.	2.5 cm.	3.0 cm.	47 gm.	5 cc.
Right kidney...	16.00 cm.	8.0 cm.	7.5 cm.	52 gm. (empty)	400 cc.

"The nitrogen content of the urine from the left kidney was: urea nitrogen 0.0045 Gm. in 1 cc.; nonprotein nitrogen, 0.0065 Gm. in 1 cc. The nitrogen content of the urine from the right kidney was: urea nitrogen, 0.0039 Gm. in 1 cc.; nonprotein nitrogen, 0.0068 Gm. in 1 cc."

In the first of the foregoing experiments, a kidney injured by a complete ureteral obstruction lasting twenty-one days has in a period of repair of two hundred and forty-nine days become an organ weighing 15 Gm., which is about one-third the weight of its hypertrophic mate. Although the excretion of phenolsulphonphthalein was only 7.5 per cent in one-half hour, still, the experiment can hardly be considered as one in which the injured kidney has gone on to complete atrophy. Whether this kidney would have become completely atrophied after a longer period of competition, it is impossible to say. Our experiments do not indicate that this would have occurred. The second experiment shows that a markedly damaged hydronephrotic kidney possesses a remarkable power to undergo repair and hypertrophy if the functional demand is placed on it.

Should the theory of renal counterbalance become established, its clinical application would be of far-reaching importance. It would play a rôle in many types of renal surgery, for if the injury to one kidney

were continued over a sufficiently long period of time to allow the opposite kidney to become fully hypertrophied, the injured kidney would eventually go on to complete atrophy even though the injurious agent were removed. It would be useless, therefore, to carry out plastic operation on a hydronephrotic kidney if its mate had become fully hypertrophied. The plastic operation would have to be supplanted by a removal of the hydronephrotic kidney, since any operation for the relief of an obstruction would be useless so far as restoration of function in that kidney would be concerned. The theory would find application also in cases of unilateral stone in which there was destruction of parenchyma in the involved kidney and accompanying hypertrophy in its mate. The operation of pyelotomy or nephrotomy would be supplanted here by nephrectomy. Also in the treatment of bilateral nephrolithiasis the period of time between the operations for the removal of the stones from each kidney should not be long enough to allow one kidney to undergo hypertrophy.

EXPERIMENTAL TECHNIC

The experiments reported in this paper were conducted on healthy dogs and were of three types. A kidney (in our experiments always the right) was damaged by producing a complete obstruction of its ureter. The obstruction was temporary and its duration varied from twelve to nineteen days. In one group of experiments the animals were killed at the end of the period of obstruction so that the changes in the obstructed and nonobstructed kidneys could be studied. In all the other experiments, the right ureter was implanted into the bladder after the temporary period of obstruction. In one group of these experiments the hypertrophied mate was removed several days after the obstruction was relieved, while in another group the hypertrophied kidney was allowed to remain undisturbed.

In all the experiments, observations of the gross and of the histologic changes in the kidneys were made. Only those experiments are reported in which there was no evidence of renal infection or in which there was simply a mild degree of pyelonephritis. In practically all the experiments, preoperative and postoperative studies of the blood urea were made.

Each operation was carried out under strictly aseptic precautions. Open ether anesthesia was used, preceded by a subcutaneous injection of 0.015 Gm. of morphine. The operative procedures are described in detail in the following paragraphs, and to avoid repetition will be referred to in the protocols only by name.

Ligation of Ureter.—The abdomen was opened through a suprapubic midline incision about 4 cm. long. The bladder was brought into the wound, and the right ureter was isolated close to the bladder. Here the ureter was doubly ligated with silk and cut between ligatures. The structures were replaced in the abdominal cavity, and the wound was closed in layers with silk.

Implantation of the Ureter into the Bladder.—The hydronephrosis was relieved in each experiment by implanting the ureter into the bladder. The abdomen was opened through a right rectus incision. The bladder was elevated into the wound, and the proximal end of the ureter was isolated. It was dissected free for about 2 cm.; its ligated end was excised, and, after allowing the urine to drain off, the end of the ureter was split longitudinally for about 0.5 cm. A suture of fine

catgut was placed in each end of the split ureter. An incision about 6 mm. long was made through the posterior wall of the bladder, and through this opening the ends of the ureter were inserted. The split ends of the ureter were then separated in opposite directions and the sutures of catgut were completed by passing each end through the wall of the bladder and were tied. The incision in the wall of the bladder was closed around the ureter and one or two sutures were passed between the bladder and the adventitia of the ureter. Care was taken to avoid obstruction at the new ureteral orifice. The structures were replaced in the abdominal cavity and the wound was closed in layers with silk.

Nephrectomy.—The left kidney was removed through either a left rectus or a left lumbar incision. The kidney was freed and delivered; the ureter and renal vessels were doubly ligated and cut between ligatures. The wound was approximated in layers with silk.

EFFECTS ON KIDNEYS OF THIRTEEN TO SIXTEEN DAY PERIODS OF UNILATERAL COMPLETE URETERAL OBSTRUCTION

PROTOCOL 1.—In dog A 51, a male mongrel, weighing 17.9 Kg., hydronephrosis was produced for sixteen days.

Sept. 23, 1927: The right ureter was ligated.

October 9: The dog was killed to obtain specimens of the kidneys after sixteen days of complete ureteral obstruction. The results of the general necropsy were negative. The right kidney showed a marked degree of hydronephrosis and dilatation of the ureter. The left kidney showed compensatory hypertrophy. The weights and measurements of the kidneys were:

	Right	Left
Weight	59.0 Gm.	76.8 Gm.
Length	7.5 cm.	7.5 cm.
Transverse diameter	4.9 cm.	5.2 cm.
Anteroposterior diameter	2.8 cm.	3.6 cm.
Capacity of pelvis	43.0 cc.	3.5 cc.
Cortex	7.0 mm.	10.0 mm.

The appearance of the kidneys is shown in figure 1. The pyelogram of the right kidney (fig. 2) showed a marked dilatation of the pelvis, calices and ureter, and a definite thinning of the parenchyma. The pyelogram of the left kidney was normal.

Histologic Observations.—In the left kidney, there was a diffuse hyperemia, particularly of the glomeruli which appeared very large, with occasional collections of serum precipitate in the capsular spaces.

In the right kidney, the glomeruli appeared concentrated in comparison to their distribution in the left kidney. The glomerular tufts showed no pathologic change, but occasionally there were small amounts of serum precipitate in the capsular spaces. There were patchy areas of tubular dilatation and widespread tubular atrophy. The tubular dilatation was most marked in the superficial zone of the cortex which was also the seat of interstitial fibrosis.

PROTOCOL 2.—In dog A 52, a white female mongrel, weighing 12.4 Kg., hydronephrosis was produced for fourteen days.

Sept. 29, 1927: The right ureter was ligated.

October 13: The dog was killed to obtain specimens of the kidneys after fourteen days of complete ureteral obstruction. The results of the general

necropsy were negative. The right kidney was hydronephrotic, and its ureter was dilated. The left kidney showed compensatory hypertrophy. The weights and measurements of the kidneys were:

	Right	Left
Weight	55.4 Gm.	56.0 Gm.
Length	8.0 cm.	7.2 cm.
Transverse diameter	4.5 cm.	4.6 cm.
Anteroposterior diameter	3.2 cm.	2.8 cm.
Capacity of pelvis	20.0 cc.	...
Cortex	7.0 mm.	8.0 mm.

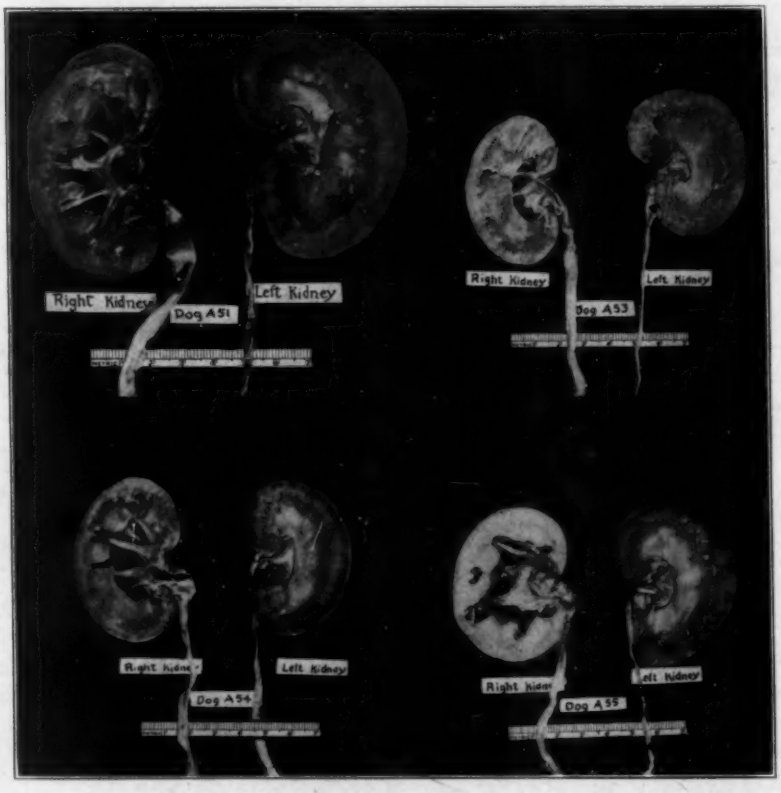

Fig. 1.—Appearance of kidneys after complete obstruction of the right ureter for sixteen, fourteen, thirteen and thirteen days, respectively, showing the marked damage (table 1).

The pyelogram of the right kidney (fig. 2) showed a moderate dilatation of the ureter and a marked dilatation of the pelvis and calices. The pyelogram of the left kidney was normal.

Histologic Observations.—The glomeruli in the left kidney were large, and occasional collections of serum precipitate were observed in the capsular spaces. The tubules showed no pathologic change. There was marked hyperemia of both cortex and medulla.

The glomeruli in the right kidney were uniformly small and in many of them there was partial or complete necrosis of the tufts (fig. 3). The necrotic portions

had a granular basophilic appearance with fragmentation and pyknosis of nuclei. In some instances, only a small fragment of the tuft was left intact and the capsular space contained a large amount of granular débris. There was widespread collapse and atrophy of tubules, which was particularly prominent in the superficial zone of the cortex. There was some slight diffuse increase of interstitial connective tissue.

PROTOCOL 3.—In dog A 53, a male mongrel, weighing 12.7 Kg., hydronephrosis was produced for fourteen days.

Sept. 29, 1927: The right ureter was ligated.

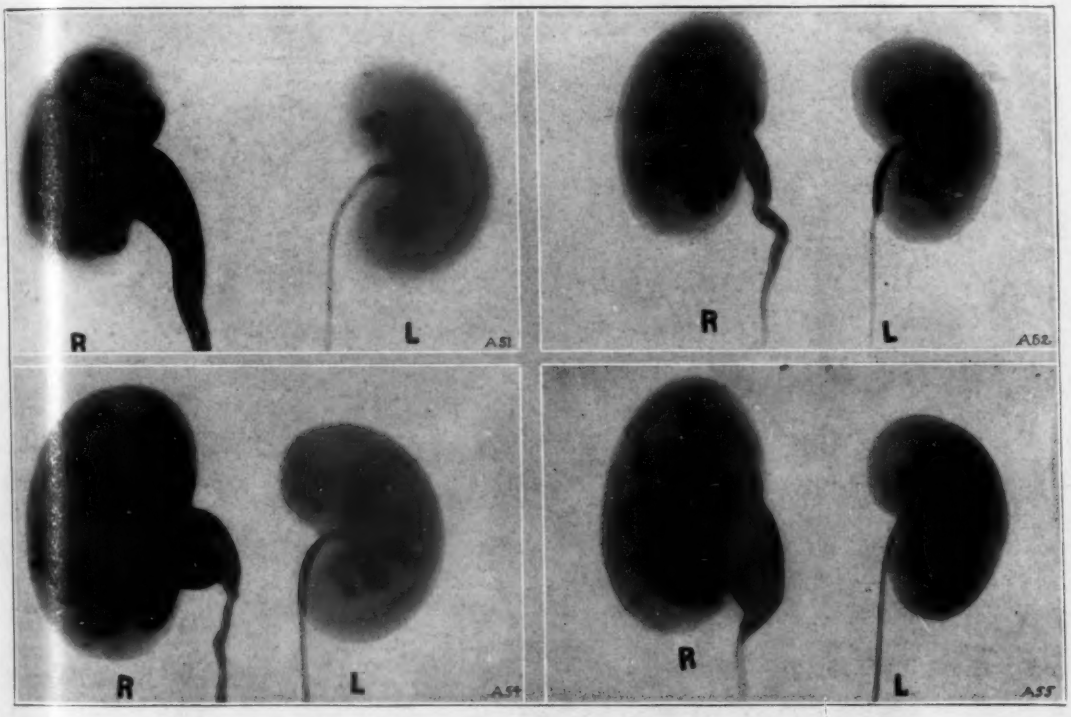

Fig. 2.—Pyelograms of kidneys after complete obstruction of the right ureter for sixteen, fourteen, thirteen and thirteen days, respectively.

October 13: The dog was killed to obtain specimens of the kidneys after a period of fourteen days of complete ureteral obstruction. The results of the general necropsy were essentially negative. The right kidney was distinctly hydronephrotic with dilatation of the ureter. Its urine showed no evidence of infection. The left kidney appeared to be hypertrophic. The weights and measurements of the kidneys were:

	Right	Left
Weight	31.4 Gm.	47.0 Gm.
Length	6.7 cm.	6.4 cm.
Transverse diameter	3.8 cm.	5.0 cm.
Anteroposterior diameter	2.4 cm.	2.9 cm.
Cortex	4.0 mm.	7.0 mm.

The appearance of the kidneys is shown in figure 1.

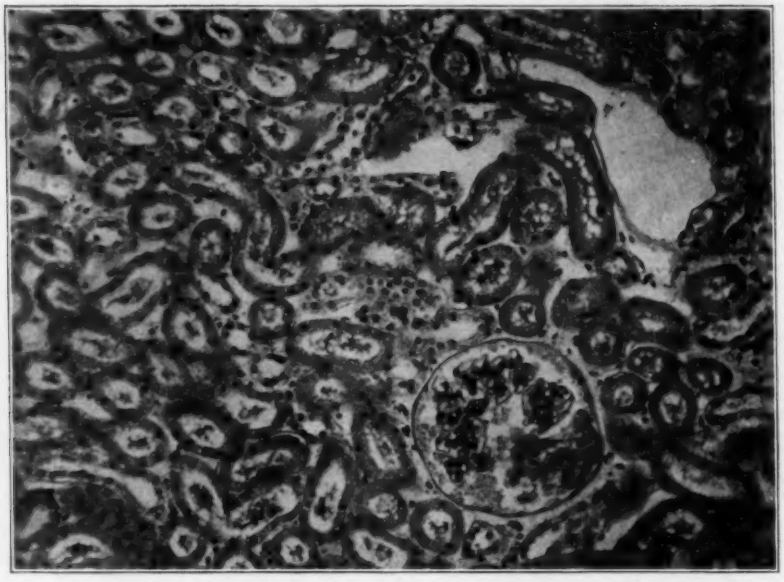

Fig. 3.—Cortex of right kidney of dog A 52, protocol 2, showing necrosis of a portion of a glomerular tuft; × 65.

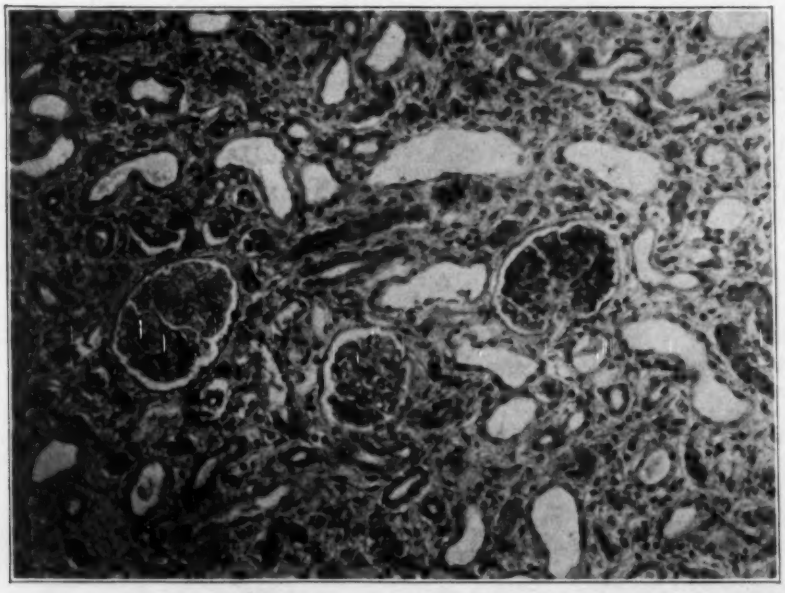

Fig. 4.—Cortex of right kidney of dog A 53, protocol 3, showing a partially necrotic glomerular tuft and many atrophic, collapsed tubules. There is a diffuse increase in interstitial fibrous connective tissue and dilatation of the loops of Henle; × 65.

Histologic Observations.—The glomeruli in the left kidney appeared larger than normal, and the tufts were distended with red blood cells. Many glomeruli showed collections of serum precipitate in the capsular spaces. The tubules appeared normal except for swelling and granularity of the epithelium. The interstitial tissue was moderately edematous. Both cortex and medulla were hyperemic.

In comparison to the left kidney, there appeared to be a concentration of glomeruli in the right kidney, especially in the superficial zone of the cortex. Some of the glomeruli appeared normal, but a great many manifested varying degrees of degenerative changes ranging from pyknosis of a few nuclei to necrosis of the entire tuft (fig. 4). There was marked tubular atrophy, many of the tubules being represented only by a small solid group of epithelial cells surrounded by a basement membrane. Occasional dilated tubules were seen. There was diffuse increase of interstitial fibrous connective tissue which was most pronounced in the medulla and in the cortex corticis.

PROTOCOL 4.—In dog A 54, a young male hound, weighing 9.8 Kg., hydronephrosis was produced for thirteen days.

Sept. 30, 1927: The right ureter was ligated.

October 13: The dog was killed to obtain specimens of the kidneys after a period of thirteen days of complete ureteral obstruction. The results of the general necropsy were negative. The right kidney was large and hydronephrotic and the ureter was dilated. The urine from this kidney showed no evidence of infection. The left kidney appeared to be normal but somewhat hypertrophic. The weights and measurements of the kidneys were:

	Right	Left
Weight	48.5 Gm.	61.8 Gm.
Length	7.5 cm.	6.8 cm.
Transverse diameter	4.8 cm.	5.0 cm.
Anteroposterior diameter	2.0 cm.	2.7 cm.
Cortex	3.5 mm.	6.0 mm.
Capacity of pelvis	80.0 cc.	...

The appearance of the kidneys is shown in figure 1. The pyelogram of the right kidney (fig. 2) showed a very marked degree of hydronephrosis with a thin parenchyma. The pyelogram of the left kidney was normal.

Histologic Observations.—The glomeruli in the left kidney were large and the tufts hyperemic and usually completely filled the capsular spaces. The capsules occasionally contained a small amount of serum precipitate. There was moderate parenchymatous degeneration of the tubular epithelium. Both cortex and medulla were intensely hyperemic, and the tubules were widely separated by distended capillaries and edematous interstitial connective tissue.

The changes in the right kidney were essentially the same as those in the right kidney of dog A 53 (protocol 3), except that there was more widespread degeneration of glomeruli and many glomeruli with normal appearing tufts showed proliferation of capsular epithelium. The pyramids were the seat of pronounced tubular atrophy and fibrosis.

PROTOCOL 5.—In dog A 55, a young female hound, weighing 8.7 Kg., hydronephrosis was produced for thirteen days.

Sept. 30, 1927: The right ureter was ligated.

October 13: The dog was killed for specimens of the kidneys after a period of thirteen days of complete ureteral obstruction. The results of the general necropsy were negative. The right kidney was markedly hydronephrotic, and its ureter was dilated. The urine showed no evidence of infection. The left kidney

was darker and more congested than the right and appeared to be hypertrophic. The weights and measurements of the kidneys were:

	Right	Left
Weight	45.0 Gm.	46.0 Gm.
Length	8.2 cm.	6.6 cm.
Transverse diameter	4.8 cm.	3.4 cm.
Anteroposterior diameter	2.4 cm.	2.6 cm.
Cortex	5.0 mm.	8.0 mm.
Capacity of pelvis	50.0 cc.	...

The appearance of the kidneys is shown in figure 1. The pyelogram of the right kidney (fig. 2) showed a marked degree of hydronephrosis. The pyelogram of the left kidney was normal.

Histologic Observations.—Left Kidney: The glomeruli were large, and the tufts were plump and in most instances filled their capsules. Occasional glomeruli showed partial necrosis of the tuft, manifested by loss of nuclei with granular degeneration of the cytoplasm. There was a moderately severe parenchymatous degeneration of the tubular epithelium. The interstitial tissue was edematous and hyperemic.

TABLE 1.—*Data on Dogs Following Unilateral Complete Ureteral Obstruction*

Protocol	Duration of Complete Obstruction of Right Ureter, Days	Weight of Kidneys, Gm.		Percentage of Total Renal Mass	
		Right	Left	Right	Left
1 (Dog A 51)	16	59.0	76.8	43.4	56.6
2 (Dog A 52)	14	55.4	56.0	49.7	50.3
3 (Dog A 53)	14	31.4	47.0	40.0	60.0
4 (Dog A 54)	13	48.5	61.8	43.9	56.1
5 (Dog A 55)	13	45.0	46.0	49.5	50.5

In the right kidney, there was a concentration of glomeruli in the subcapsular zones of the cortex and many of them were partially or completely necrotic. The tubules were predominantly atrophic although a few distended loops were seen. Parenchymatous degeneration of tubular epithelium was present. In general, the sections appeared very similar to those from the right kidneys of dogs A 53 and A 54 (protocols 3 and 4).

These five experiments are recorded to show the effects on the kidneys of periods of from thirteen to sixteen days of unilateral complete ureteral obstruction. It can be seen from the descriptions and illustrations (figs. 1 and 2) that a fairly marked degree of hydronephrosis and renal damage was produced by the ureteral obstruction. The relatively slight differences in weight between the hydronephrotic right kidney and the hypertrophic left kidney are striking and especially interesting when compared with the relative weights of the kidneys of some of the other experiments.

A summary of the histologic changes observed in this group of experiments follows:

The undisturbed left kidneys of these animals were fairly uniform in their histologic appearances. Both cortex and medulla were intensely

hyperemic with considerable interstitial edema, particularly of the cortex. The glomeruli were large, and the hyperemic tufts tended to fill their capsular spaces. The presence of serum precipitate within the glomerular capsule was a common occurrence.

The obstructed right kidneys showed considerable variation in the extent of the pathologic changes. The earliest change was manifested in the tubules and interstitial tissue (fig. 4). Dilatation as well as atrophy and collapse of tubules, with interstitial edema, was seen in kidneys showing no glomerular damage. The extent of tubular atrophy varied but was most marked in those kidneys showing glomerular damage. The glomerular changes consisted of partial or complete necrosis of the tufts (figs. 3 and 4). The number of tufts damaged varied in different animals but in none of them did the damaged tufts outnumber those that appeared normal. The necrosis manifested itself by a basophilic, granular degeneration of the cytoplasm with pyknosis, fragmentation, and disappearance of nuclei. Occasional masses of granular cellular débris were present in the capsular spaces around necrotic tufts. In one animal there was moderate proliferation of the capsular epithelium. There was a diffuse increase in interstitial fibrous connective tissue, most pronounced in the medulla and in the subcapsular zone of the cortex. In the fibrosed outer zone of the cortex proper the glomeruli appeared especially numerous, and it was in these concentrated glomeruli that the most severe damage was manifest.

REPAIR OF HYDRONEPHROTIC KIDNEYS WITH REMOVAL OF HYPERTROPHIC MATE

PROTOCOL 6.—In dog A 20, a female collie, weighing 14 Kg., hydronephrosis was produced for eleven days followed by a period of repair of eight hundred and twenty-eight days.

Jan. 9, 1925: The blood urea was 38 mg. per hundred cubic centimeters.

January 13: The blood urea was 23 mg. The right ureter was ligated.

On January 15, the blood urea was 14.1 mg.; on January 22, 50.1 mg.

January 24: The right ureter was implanted into the bladder after a period of eleven days of complete ureteral obstruction.

January 26: The blood urea was 33 mg. Left nephrectomy was performed. The left kidney appeared to be grossly normal although it was somewhat hypertrophied. The weight and measurements were: weight, 34.5 Gm.; length, 6 cm.; transverse diameter, 3.8 cm.; anteroposterior diameter, 2.8 cm.; cortex, 7 mm.

February 3: The blood urea was 140.4 mg., but in spite of this the dog appeared to be in good general condition.

On February 9, the blood urea was 112.3 mg.; February 13, 102 mg.; February 26, 69 mg.; March 16, 40.2 mg.; March 25, 66.8 mg.; April 1, 53.5 mg.; April 10, 53.5 mg.; May 7, 62.5 mg.; June 25, 27 mg.; July 22, 43.2 mg. (condition excellent); September 24, 44 mg.; October 16, 37 mg.; November 13, 42 mg.; December 23, 80 mg.

Jan. 4, 1926: The dog gave birth to a litter of seven pups.

January 14: Her general condition was excellent. The blood urea was 68.5 mg.

On February 13, the blood urea was 44.5 mg.; March 17, 57.8 mg.; June 24, 68.4 mg.; August 17, 37 mg.

September 1: The dog gave birth to a litter of seven pups.

On October 13, the blood urea was 32 mg.; November 19, 53 mg.

December 23: The microscopic examination of the urine showed no pus cells, red blood cells or casts.

On Jan. 24, 1927, the blood urea was 54 mg.; March 4, 41 mg.; April 26, 36 mg.

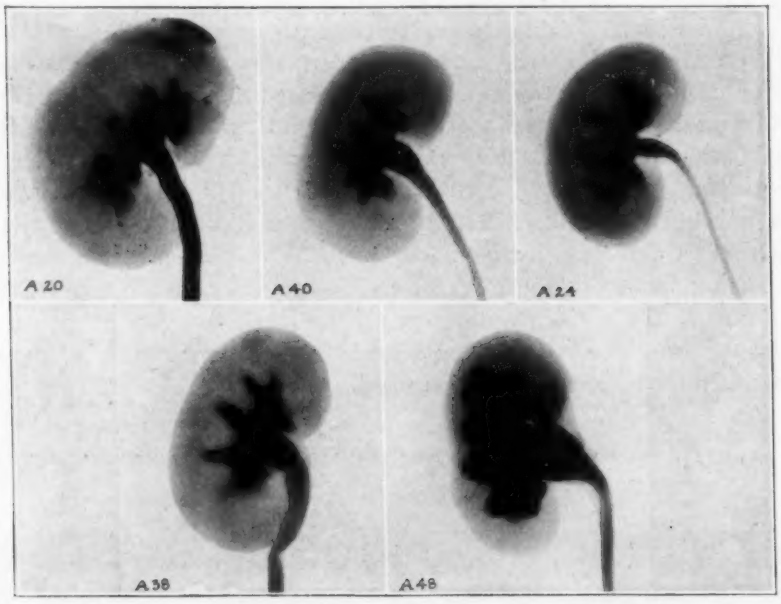

Fig. 5.—Pyelograms of the obstructed right kidneys of dogs A 20, A 40, A 24, A 38 and A 48, showing a tendency of the pelves to return to normal shape and size.

May 2: For the past few days the dog appeared sick, and on this date she was found dead in the kennels.

Necropsy.—There were no external signs of violence. The heart was normal. The lungs showed some small patches of pneumonia. On opening the abdominal cavity, about 100 cc. of dark fluid was found. All the abdominal organs except the pancreas and kidneys were normal. The former showed definite gross and microscopic evidence of an acute pancreatitis. The left kidney had been removed at a previous operation. The right kidney appeared to be hypertrophic. Its ureter was slightly dilated at its upper portion for a distance of about 4 cm. but below this it was normal. The anastomosis of the ureter into the bladder was satisfactory and appeared to be perfectly patent. The bladder was normal. The weight and measurements of the right kidney were: weight, 58.2 Gm.; length, 7.5 cm.; transverse diameter, 5 cm.; anteroposterior diameter, 3 cm.; capacity of pelvis,

5.9 cc.; cortex, 4 mm. A pyelogram showed a slight degree of dilatation of the upper portion of the ureter and the pelvis, but was otherwise not remarkable except that a small amount of the sodium iodide had extravasated into the parenchyma in the region of the lower pole (fig. 5). The gross appearance of the kidneys is shown in figure 6.

Histologic Observations.—The glomeruli in the left kidney appeared large with plump, hyperemic tufts which filled their capsules completely. There was a moderate degree of parenchymatous degeneration of the tubular epithelium. Otherwise, there was no pathologic change.

The histologic examination of the right kidney was rendered somewhat unsatisfactory by the amount of postmortem change present. The glomeruli were very large and hypertrophic, with plump cellular tufts which filled their capsules. The usual difference in size between peripheral and central glomeruli was not present and those in the outer zone of the cortex were as large as those in the corticomedullary zone. A few thickened capsules were seen. There was a mild, patchy chronic pyelonephritis, and in the densely infiltrated radial scars the glomeruli were fibrosed and atrophic and the tubules filled with pus cells.

PROTOCOL 7.—In dog A 33, a white and brown female mongrel, weighing 7 Kg., hydronephrosis was produced for fifteen days, followed by a period of repair of five hundred and five days.

On May 18, 1925, the blood urea was 25.5 mg. per hundred cubic centimeters, and on May 25, 47 mg.

May 25: The right ureter was ligated.

On May 27, the blood urea was 49 mg.; on June 9, 33 mg.

June 9: The ureter was implanted into the bladder after a period of fifteen days of complete ureteral obstruction.

June 11: The blood urea was 25 mg. Left nephrectomy was performed. The left kidney appeared grossly normal. The weight and measurements were: weight, 38 Gm.; length, 5.1 cm.; transverse diameter, 3.6 cm.; anteroposterior diameter, 2.5 cm.; cortex, 6 mm.

On June 15, the blood urea was 174.4 mg., but the general condition of the dog seems good. On June 24, it was 80 mg.; on July 8, 76.9 mg.

July 30: The dog gave birth to a litter of five pups.

On September 24, the blood urea was 24 mg.; November 13, 52 mg.; Feb. 13, 1926, 87.7 mg.; March 17, 67.6 mg.; April 29, 65.3 mg.; June 3, 70.2 mg.; June 24, 67.6 mg.; August 16, 23 mg.; October 13, 37 mg.

October 27: The dog was killed in a fight.

Necropsy: The dog sustained extensive wounds of the thoracic wall and right lumbar region. Through the lumbar wound the right kidney had been somewhat lacerated. Aside from these wounds, the results of the necropsy were negative. The right kidney, aside from its lacerations, appeared to be normal. It was firm on palpation and the cut surface showed a normal medulla and cortex. The pelvis and ureter were not dilated. The implantation of the ureter into the bladder was satisfactory and appeared to be perfectly patent. The weight was 32 Gm., and the cortex measured 6 mm.

The gross appearance of the kidneys is shown in figure 6.

Histologic Observations.—In the left kidney, there was diffuse hyperemia and the glomerular tufts were plump, filling their capsules. The tubular epithelium was the seat of moderate parenchymatous degeneration.

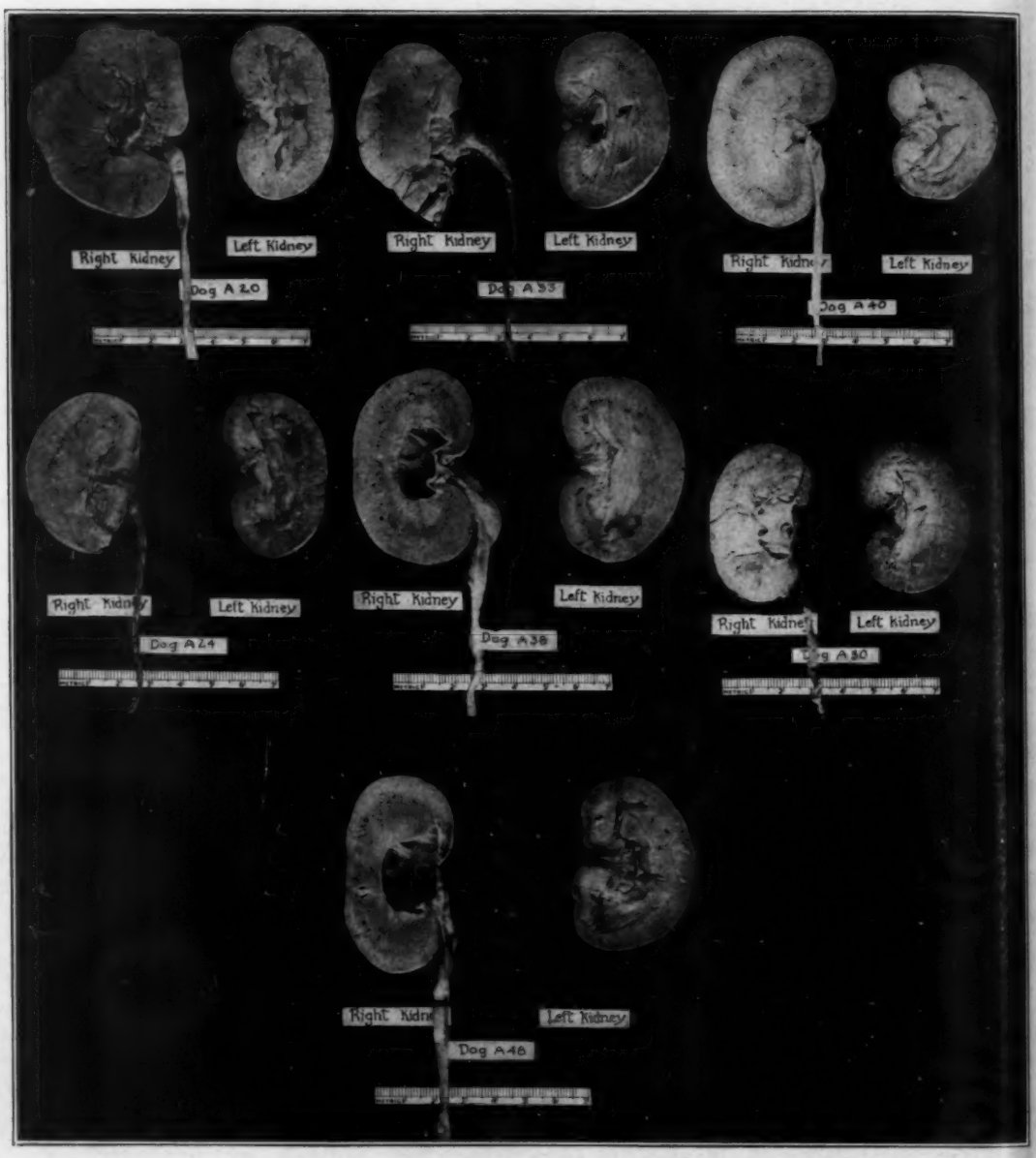

Fig. 6.—Appearance of kidneys of experiments of group II, showing the repair and hypertrophy which the hydronephrotic right kidney undergoes after removal of its mate (table 2).

In the right kidney, most of the glomeruli were large and hypertrophic, and there was a collection of serum precipitate within the capsules of many of them. Occasional small fibrosed glomeruli with thickened capsules were encountered. There was no evidence of interstitial fibrosis. The normal architecture was preserved.

PROTOCOL 8.—In dog A 40, a male mongrel, weighing 10.3 Kg., hydronephrosis was produced for fifteen days, followed by a period of repair of two hundred and ninety-three days.

On May 18, 1925, the blood urea was 25.5 mg. per hundred cubic centimeters.

May 25, 1925: The right ureter was ligated. On May 27, the blood urea was 51 mg.; on June 9, 34 mg.

June 9: The ureter was implanted into the bladder after fifteen days of complete ureteral obstruction.

June 11: The blood urea was 31.2 mg.

June 11: Left nephrectomy was performed. The left kidney appeared somewhat hypertrophied but otherwise normal. The weight and measurements were: weight, 36.7 Gm.; length, 6 cm.; transverse diameter, 3.8 cm.; anteroposterior diameter, 2.6 cm.; cortex, 5 mm.

On June 15, the blood urea was 144 mg., but the animal's general condition seems to be good. On June 24, it was 59 mg.; July 8, 54 mg. (weight, 9.3 Kg.); July 31, 59.1 mg.; August 13, 51 mg.; September 24, 48 mg.; October 16, 45 mg.; November 13, 43 mg.; December 23, 50 mg.; Jan. 14, 1926, 52 mg.; February 13, 29.5 mg.; March 17, 47 mg.

March 29: The dog was killed.

Necropsy.—The results of necropsy were negative except the changes found in the urinary tract. The right kidney appeared to be normal and somewhat hypertrophied. The right ureter was slightly dilated. The implantation of the ureter into the bladder was satisfactory and perfectly patent. The weight and measurements of the right kidney were: weight, 40.6 Gm.; length, 6.4 cm.; transverse diameter, 3.8 cm.; anteroposterior diameter, 2.5 cm.; cortex, 5 mm.; capacity of pelvis, 4 cc. A pyelogram appeared relatively normal except for the slight dilatation of the ureter and pelvis (fig. 5). The gross appearance of the kidneys is shown in figure 6.

Histologic Observations.—Except for the general glomerular hypertrophy and the presence of occasional fibrosed, atrophic glomeruli with thickened capsules in the right kidney there was no histologic difference in the two kidneys of this animal. There was no scarring or increase in interstitial fibrous connective tissue.

PROTOCOL 9.—In dog A 24, a brown and white, short haired, male mongrel, weighing 9 Kg., hydronephrosis was produced for twelve days followed by a period of repair of one hundred and fifty-five days.

On Jan. 22, 1925, the blood urea was 43 mg.; on January 27, 27 mg.

January 30: The right ureter was ligated.

On February 3, the blood urea was 32 mg.; on February 9, 44 mg.

February 11: The right ureter was implanted into the bladder after a period of twelve days of complete ureteral obstruction.

February 13: The blood urea was 43 mg.

February 13: Left nephrectomy was performed. The kidney appeared somewhat hypertrophied but otherwise normal. The weight and measurements were: weight, 30.9 Gm.; length, 6 cm.; transverse diameter, 3.7 cm.; anteroposterior diameter, 2.9 cm.; cortex, 6 mm.

On February 16, the blood urea was 85.1 mg.; February 26, 47 mg.; March 9, 24.9 mg.; March 25, 40.2 mg.; April 1, 40.2 mg.

April 10: The dog had been losing weight and had mange. On this date it weighed 6.5 Kg. The blood urea was 43.2 mg.

April 16: The dog's condition seemed better. The blood urea was 24 mg.

May 7: The blood urea was 46 mg.

June 25: The dog was in good condition. The blood urea was 33 mg.

July 14: The dog was killed.

Necropsy.—No abnormalities were found in any of the organs except those of the urinary tract. The right kidney was grossly normal except that it appeared somewhat hypertrophied. The implantation of the ureter into the bladder was satisfactory and perfectly patent. The right ureter and pelvis appeared to be normal. The weight and measurements of the kidney were: weight, 34.1 Gm.; length, 6.1 cm.; transverse diameter, 3.6 cm.; anteroposterior diameter, 2.6 cm.; cortex, 5 mm.; capacity of pelvis, 3.5 cc. A pyelogram showed no abnormalities (fig. 5). The appearance of the kidneys is shown in figure 6.

Histologic Observations.—In the left kidney, the glomeruli were plump and hyperemic, and occasional collections of serum precipitate were present in the capsular spaces.

In the right kidney, there was no evidence of interstitial fibrosis in the cortex. The glomeruli appeared normal except for serum precipitate in the glomerular spaces. The arcuate arteries showed a zone of peri-arterial fibrosis. There was a moderate diffuse increase of fibrous connective tissue in the pyramids.

Protocol 10.—In dog A 38, a black and white female mongrel, weighing 16 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of seventy-nine days.

May 18, 1925: The blood urea was 43.3 mg. per hundred cubic centimeters.

May 20: The right ureter was ligated.

On May 25, the blood urea was 54.5 mg.; on June 3, 47 mg.

June 5: The right ureter was implanted into the bladder after a period of sixteen days of complete ureteral obstruction.

June 8: The blood urea was 43.2 mg.

June 8: Left nephrectomy was performed. The kidney appeared hypertrophied but was otherwise normal. The weight and measurements were: weight, 45.1 Gm.; length, 6.6 cm.; transverse diameter, 3.8 cm.; anteroposterior diameter, 2.7 cm.; cortex, 7 mm.

On June 15, the blood urea was 161 mg.; June 24, 76 mg.; July 8, 62.4 mg.

July 31: The animal's condition was poor. She appeared thin, weak and mangy. The blood urea was 108 mg.

August 13: The dog's general condition seemed much better. The blood urea was 122.1 mg.

August 23: The animal was found dead in the kennels.

Necropsy.—No definite cause of death was found. All the organs seemed normal. The weight and measurements of the right kidney were: weight, 44.5 Gm.; length, 6.2 cm.; transverse diameter, 3.8 cm.; anteroposterior diameter, 2.7 cm.; cortex, 4 mm. The anastomosis of the ureter into the bladder was perfectly patent. The ureter and pelvis were somwhat dilated. A pyelogram was made which, aside from some dilatation of the ureter and pelvis, was relatively normal (fig. 5). The gross appearance of the kidneys is shown in figure 6.

Histologic Observations.—The glomeruli of the left kidney were hyperemic, and many of them contained serum precipitate within the capsular spaces.

The glomeruli of the right kidney were larger than in the left kidney. There was a moderate amount of scarring in the pyramids; otherwise the two kidneys were histologically identical.

PROTOCOL 11.—In dog A 30, a brown and white male mongrel, weighing 6.9 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of forty-two days.

May 18, 1925: The blood urea was 25 mg. per hundred cubic centimeters.

May 19: The right ureter was ligated.

On May 21, the blood urea was 26.7 mg.; May 25, 51 mg.; June 3, 56 mg.

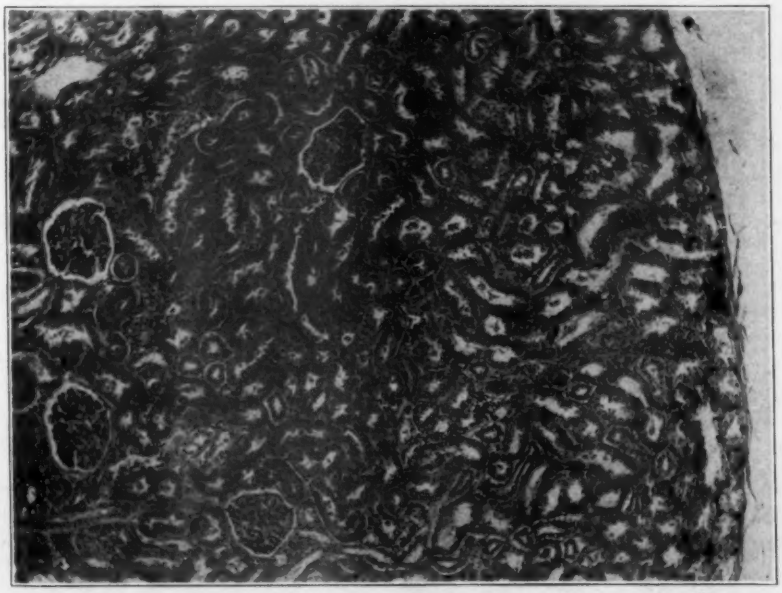

Fig. 7.—Cortex of right kidney of dog A 30, protocol 11. The right kidney was obstructed sixteen days, and two days following relief of the obstruction the left kidney was removed and the right kidney allowed a forty-two day repair period during which time it was forced to carry the entire renal function. There was no essential difference in the histologic appearance of this kidney as compared with the left; × 45.

June 4: The right ureter was implanted into the bladder after a period of sixteen days of complete ureteral obstruction.

June 6: The blood urea was 23 mg.

June 6: Left nephrectomy was performed. The kidney appeared grossly normal and weighed 27.3 Gm. The measurements were: length, 5.1 cm.; transverse diameter, 3.5 cm.; anteroposterior diameter, 2.5 cm.; cortex, 8 mm.

June 8: The blood urea was 230 mg. per hundred cubic centimeters, but the general condition seemed good in spite of this high elevation.

On June 15, the blood urea was 127 mg.; June 24, 112 mg.; July 8, 72 mg.

July 16: The dog was killed.

Necropsy.—The general observations were negative. The right kidney appeared somewhat small, and there was some definite dilatation of the ureter and pelvis still present. The weight and measurements were: weight, 22.3 Gm.; length, 5.5 cm.; transverse diameter, 3.1 cm.; anteroposterior diameter, 21 cm.; capacity of pelvis, 4.5 cc.; cortex, 6 mm. A pyelogram appeared normal except for a slight dilatation of the pelvis and ureter. The appearance of the kidneys is shown in figure 6.

Histologic Observations.—The kidneys showed no histologic abnormality and were identical in appearance except for a mild pyelonephritis and parenchymatous degeneration of tubular epithelium in the right kidney. Figure 7 shows the subcapsular cortex of the right kidney. There were no atrophic, fibrosed glomeruli in the right kidney, nor was there any interstitial fibrosis.

Protocol 12.—In dog A 48, a short haired, black and tan male mongrel, weighing 11.2 Kg., hydronephrosis was produced for nineteen days followed by a period of repair of thirty-four days.

July 1, 1925: The blood urea was 18.6 mg. per hundred cubic centimeters.

July 1: The right ureter was ligated.

July 20: The blood urea was 25.1 mg.

July 20: The right ureter was implanted into the bladder after a period of nineteen days of complete ureteral obstruction.

July 22: The blood urea was 21 mg.

July 27: Left nephrectomy was performed. The kidney appeared hypertrophied, but was otherwise normal. The weight and measurements were: weight, 47 Gm.; length, 6.6 cm.; transverse diameter, 3.9 cm.; anteroposterior diameter, 3.5 cm.; cortex, 7 mm.

August 4: The blood urea was 187.2 mg. The dog weighed 12.2 Kg.

August 23: The dog died from distemper.

Necropsy.—There were definite areas of consolidation in both lungs, but otherwise the results of the general necropsy were negative. The right kidney appeared somewhat large and showed definite dilatation of the pelvis and ureter. The anastomosis of the ureter into the bladder was patent. The weight measurements were: weight, 42.2 Gm.; length, 6.7 cm.; transverse diameter, 3.9 cm.; anteroposterior diameter, 2.6 cm.; cortex, 5.5 mm.; capacity of pelvis, 14 cc. A pyelogram showed that a fairly marked degree of hydronephrosis was still present (fig. 5). The gross appearance of the kidneys is shown in figure 6.

Histologic Observations.—Except for marked hyperemia there were no pathologic changes in the left kidney. The entire cortex and medulla of the right kidney showed a marked increase of interstitial fibrous connective tissue. This fibrosis did not have an even distribution but was most severe in the medulla and in the outer zones of the cortex with many dense radial scars. The glomeruli were condensed so that a great many were encountered in each field. Most of the glomerular tufts appeared normal as to structure although many of them were very small. They were uniformly hyperemic and in the corticomedullary zone a number of them were hypertrophic with collections of serum precipitate in the capsular spaces. Rarely small fibrosed glomeruli were seen. The tubules were generally very small in diameter, and occasional tubules were seen which were dilated and filled with red blood cells.

In this series of experiments (table 2), the right kidney was rendered hydronephrotic by complete ureteral obstruction for from eleven to nineteen days. Several days after the obstruction was relieved, the hypertrophic mate was removed so that the hydronephrotic kidney had to carry on all of the renal function.

While these experiments have no direct bearing on the question of renal atrophy of disuse, it was necessary to conduct them as control experiments in studying the problem of renal counterbalance, because, if it were demonstrated that an injured kidney did undergo progressive atrophy when allowed to remain in competition with its hypertrophic mate, it would also be essential to demonstrate that a similarly injured kidney could perform the necessary renal function if the entire load were

TABLE 2.—*Data on Dogs with Repair of Hydronephrotic Kidney and Removal of Hypertrophic Mate*

	Proctocol	Duration of Complete Obstruction of Right Ureter, Days	Interval Between Relief of Obstruction to Right Ureter and Left Nephrectomy, Days	Period of Repair of Right Kidney, Days	Weight of Kidneys, Gm.	
					Right, at Autopsy	Left, at Operation
6	(Dog A 20).....	11	2	828	58.2	34.5
7	(Dog A 33).....	15	2	505	32.0	38.0
8	(Dog A 40).....	15	2	293	40.6	36.7
9	(Dog A 24).....	12	2	155	34.1	30.9
10	(Dog A 38).....	16	3	79	44.5	45.1
11	(Dog A 30).....	16	2	42	22.3	27.3
12	(Dog A 48).....	19	7	34	42.2	47.0

thrown on it. In this way it could be indicated that the injury which had been applied to the kidney was not of itself sufficient to cause the progressive atrophy and that some other factor was necessary. These experiments show that the hydronephrotic kidney is capable of becoming a functionally good organ, and they are interesting in that they show how well an injured kidney can undergo repair and hypertrophy and carry on the entire renal function when the necessity is placed on it (figs. 5, 6 and 7).

In practically all these experiments the blood urea showed a definite elevation following the removal of the hypertrophic left kidney, but as a general rule this gradually returned to a relatively normal level. Apparently the injured right kidney could not immediately take over the entire load of renal function satisfactorily, but could do so later as it underwent repair and hypertrophy.

Histologically, the left kidneys of these animals were very hyperemic, and the glomerular tufts were plump and completely filled the capsular spaces. Occasional glomeruli contained collections of serum precipitate.

The right kidneys showed unmistakable glomerular hypertrophy which was especially well marked in those animals which were allowed the longest periods of repair after relief of the obstruction.

It would seem from the infrequency of finding damaged glomeruli or tubules even in as short a time as thirty-four days after relief of the obstruction that recovery from the injury is rapid when the entire functional load is placed on the injured kidney. This observation becomes particularly striking when the right kidneys of this series are compared with the right kidneys of series I. The only sign of injury manifested by the right kidneys of series II was diffuse interstitial fibrosis, and in animals having a repair period of forty-two days or more there was no evidence whatsoever of previous renal injury (fig. 7).

REPAIR OF THE HYDRONEPHROTIC KIDNEY WITH THE HYPERTROPHIC MATE UNDISTURBED

PROTOCOL 13.—In dog A, young black, male mongrel, weighing 12.8 Kg., hydronephrosis was produced for twelve days followed by a period of repair of eight hundred and seven days.

March 6, 1925: The preoperative blood urea was 30.5 mg. per hundred cubic centimeters. The right ureter was ligated.

On March 9, the blood urea was 43.2 mg.; March 13, 30.5 mg.; March 16, 18 mg. The dog was in excellent condition.

March 18: The right ureter was implanted into the bladder after a period of twelve days of complete ureteral obstruction.

On March 20, the blood urea was 41.6 mg.; March 25, 34 mg.; April 1, 27.2 mg.; April 16, 30 mg.; April 23, 40.2 mg.; May 7, 50 mg.; June 25, 30 mg.; July 22, 31.9 mg.; September 24, 40 mg.; October 16, 26 mg. (weight 24 Kg.); February 13, 1926, 46.8 mg.; March 17, 44.9 mg.; April 29, 26 mg.; June 3, 29.2 mg.; August 16, 28 mg.; October 13, 30 mg.; November 19, 36 mg.; Jan. 24, 1927, 47 mg.

On January 24, the microscopic examination of the urine was normal. On March 4, the blood urea was 32 mg.; on April 26, 30 mg.

June 3: The dog was first given 0.015 Gm. of morphine subcutaneously, and then 500 cc. of physiologic solution of sodium chloride was given intravenously in order to produce diuresis. With the animal under procaine hydrochloride anesthesia, the ureters were exposed and catheters were inserted into them. One cubic centimeter of phenolsulphonphthalein was given intravenously. On the left side the appearance time was four minutes, and 44 per cent of the dye was excreted in one hour in 20 cc. of urine. On the right side the appearance time was eight minutes, and 14 per cent of the dye was excreted in one hour in 14 cc. of urine. The urine from each kidney was normal. The dog was killed with magnesium sulphate injected intravenously.

Necropsy.—The dog weighed 23.2 Kg. All the organs were normal except the kidneys. The right kidney was about one-half the size of the left, but had the appearance of a functioning organ with a firm parenchyma. The anastomosis between the right ureter and the bladder was patent. The right ureter showed a moderate degree of dilatation, and there was a rather marked degree of dilatation of the extrarenal portion of the pelvis of the right kidney. The left kidney

appeared to be normal and somewhat hypertrophied. The weights and measurements of the kidneys were:

	Right	Left
Weight	40.5 Gm.	71.5 Gm.
Length	6.6 cm.	7.5 cm.
Transverse diameter	3.8 cm.	4.5 cm.
Anteroposterior diameter	2.2 cm.	2.5 cm.
Capacity of pelvis	12.0 cc.	5.0 cc.
Cortex	5.0 mm.	5.5 mm.

The appearance of the kidneys is shown in figure 8. Pyelograms of both kidneys were made (fig. 9). The pyelogram of the right kidney showed a marked dilatation of the extrarenal portion of the pelvis, but the intrarenal portion of the pelvis and the calices appeared to be relatively normal. The pyelogram of the left kidney was normal.

Histologic Observations.—The right and left kidneys were histologically identical except that the glomeruli were uniformly hypertrophic in the right. Occasional fibrosed tufts adherent to thickened capsules were seen in both kidneys, but neither showed any interstitial fibrosis nor any evidence of extensive glomerular or tubular atrophy (fig. 10).

PROTOCOL 14.—In dog A 41, a red and brown female, weighing 8.8 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of seven hundred and twenty-eight days.

May 18, 1925: The blood urea was 41.6 mg. per hundred cubic centimeters.

May 19: The right ureter was ligated.

On May 21, the blood urea was 23.5 mg., and on May 25, 35.1 mg.

June 4: The right ureter was implanted into the bladder after a period of sixteen days of complete ureteral obstruction.

On June 6, the blood urea was 29 mg.; June 15, 38.6 mg.; June 24, 35 mg.; July 8, 29.5 mg. (general condition good, weight 8.2 Kg.); July 31, 28.9 mg.; September 24, 20 mg.; October 16, 27 mg.; November 13, 33 mg.; Jan. 14, 1926, 46.8 mg.; March 17, 25.1 mg.; April 29, 22 mg.; June 3, 36.4 mg.; June 24, 44 mg.; August 16, 22 mg.; October 13, 20 mg.; November 19, 27 mg. On December 23, the microscopic examination of urine was normal. On Jan. 24, 1927, the condition of the dog was good, and blood urea was 35 mg. On March 4, it was 22 mg., and on April 26, 24 mg.

June 2: The dog was given 0.015 Gm. of morphine, subcutaneously, and 500 cc. of water was given by stomach tube to produce diuresis. With the animal under procaine hydrochloride anesthesia, both ureters were exposed and catheters were inserted into them. One cubic centimeter of phenolsulphonphthalein was injected intravenously. On the left side the appearance time was four minutes, and 50 per cent of the dye was excreted in one hour in 18 cc. of urine. On the right side the appearance time was fifteen minutes, and 10 per cent of the dye was excreted in 8 cc. of urine in one hour. The urine from each kidney was normal. The dog was killed with ether.

Necropsy.—The dog weighed 13.8 Kg. All the organs were normal except the kidneys. The right kidney was small and somewhat atrophic. The lower pole was somewhat larger than the upper one. The parenchyma was firm and seemed to consist of good renal tissue. The anastomosis between the right ureter and the bladder was patent. The right ureter showed a moderate degree of dilatation, but the kidney itself was not hydronephrotic. The left kidney appeared to be

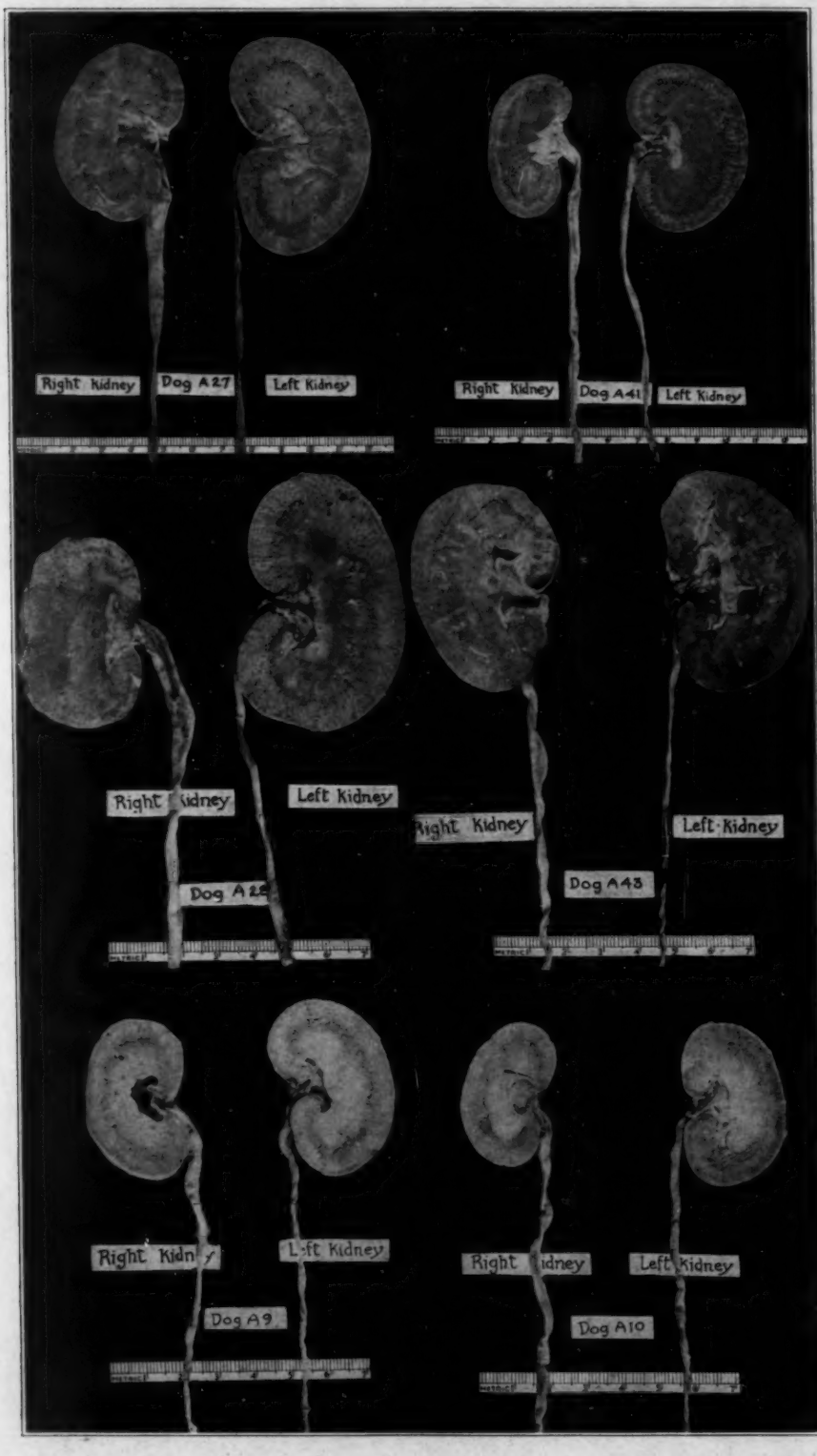

Fig. 8 A and B.—Appearance of kidneys in experiments of group III. The right ureter had been obstructed for periods varying from twelve to nineteen days following which the obstruction was relieved and the right kidney allowed to function in "competition" with its undisturbed hypertrophic mate. These photographs show that the right kidneys contain a considerable amount of renal tissue and did not undergo atrophy of disuse (table 3).

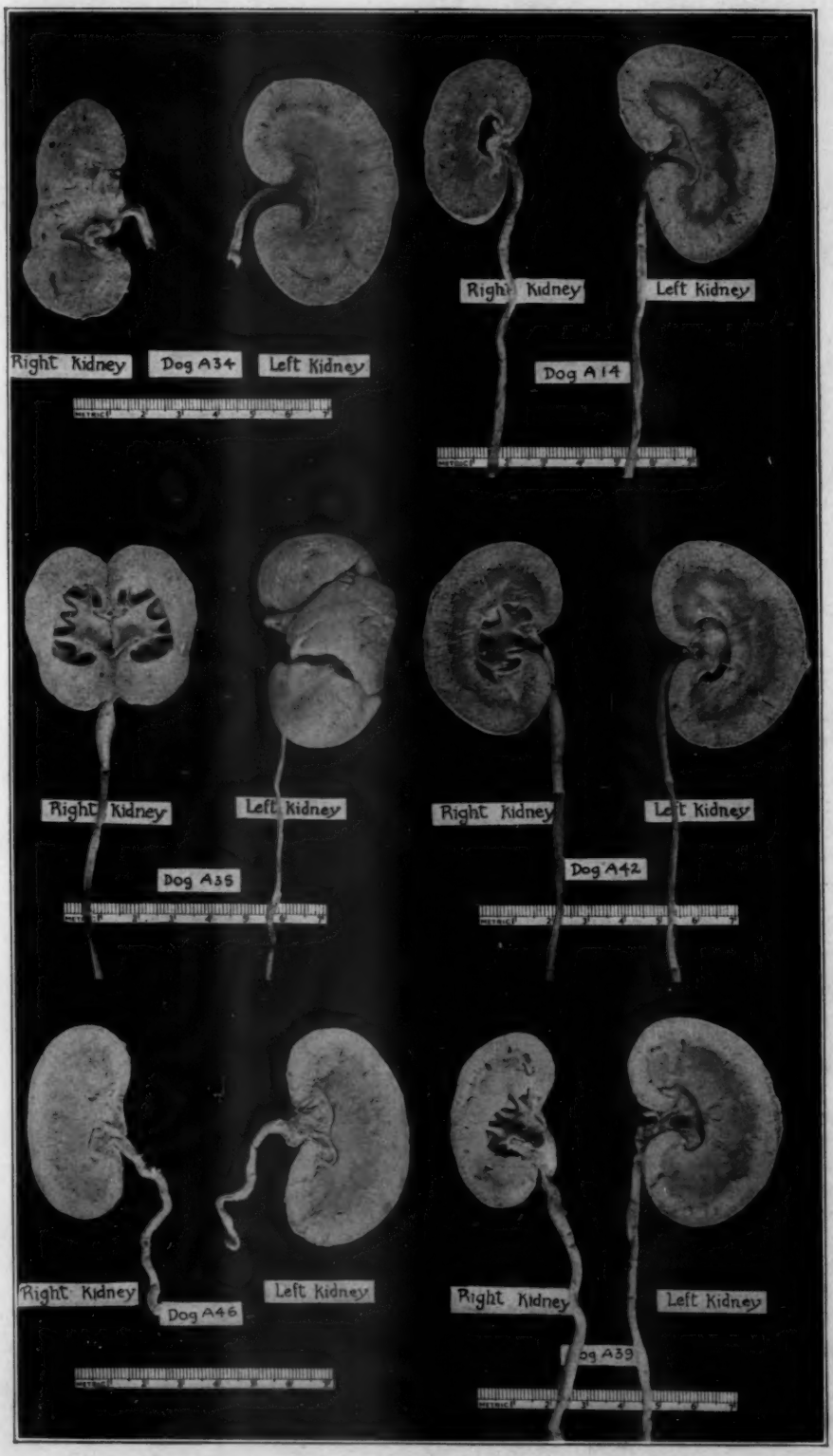
Right Kidney
Dog A34
Left Kidney
Right Kidney
Left Kidney
Dog A14
Right Kidney
Left Kidney
Dog A35
Right Kidney
Left Kidney
Dog A42
Right Kidney
Left Kidney
Dog A46
Right Kidney
Left Kidney
Dog A39

Figure 8 B.

normal and somewhat hypertrophied. The weights and measurements of the kidneys were:

	Right	Left
Weight	16.2 Gm.	48.7 Gm.
Length	5.2 cm.	6.4 cm.
Transverse diameter	2.5 cm.	4.1 cm.
Anteroposterior diameter	1.9 cm.	3.5 cm.
Capacity of pelvis	5.5 cc.	3.5 cc.
Cortex	3.0 mm.	6.0 mm.

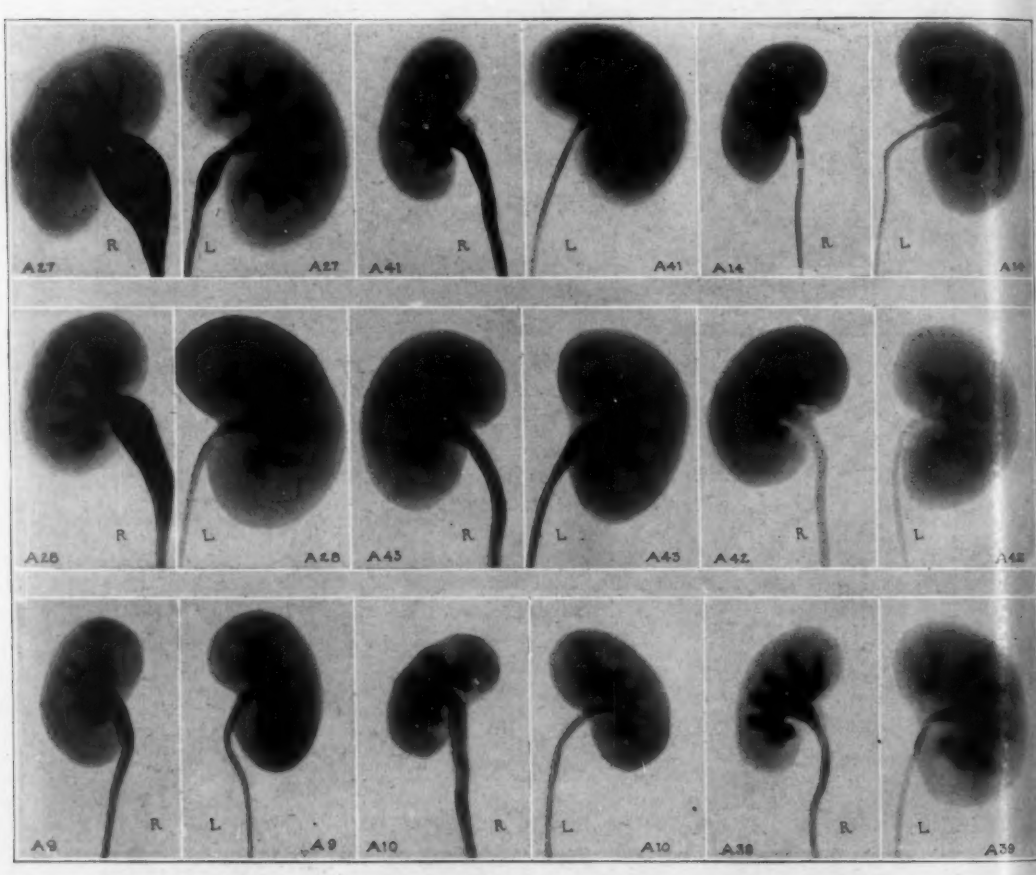

Fig. 9.—Pyelograms of the right and left kidneys of the experiments of group III. These show a tendency of the hydronephrotic pelvis to return to normal although the ureter frequently remained dilated.

The appearance of the kidneys is shown in figure 8.

Pyelograms were made of each kidney (fig. 9). Except for the dilatation of the ureter and extrarenal portion of the pelvis and some extravasation of the sodium iodide in the region of the upper pole, the pyelogram of the right kidney was essentially normal. The pyelogram of the left kidney showed nothing abnormal.

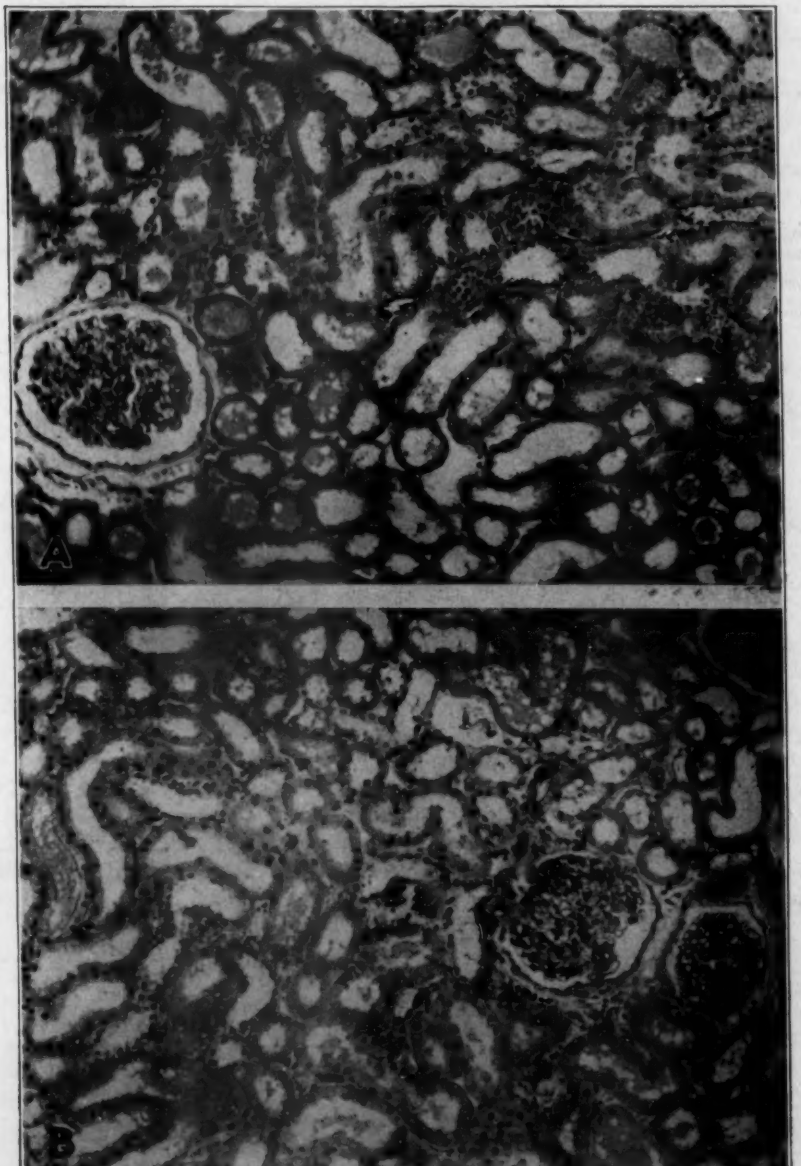

Fig. 10.—Sections from the cortex of the right and left kidneys of dog A 27, protocol 13. The right kidney was obstructed for sixteen days and then allowed a repair period of eight hundred seven days, working in "competition" with the undisturbed left kidney. There were no important histologic differences between the right and left kidneys; × 65. *A* indicates the right kidney; *B*, the left.

Histologic Observations.—A few hyalinized glomeruli were present in the left kidney, and many of the glomeruli contained a small amount of serum precipitate within the capsular spaces. Hyaline tubular casts were frequent. In one slide a small abscess was seen in the cortex just beneath the capsule.

In the right kidney, the cortex corticis had entirely disappeared and occasional glomeruli were seen in the most peripheral portions of the cortex. Just beneath the capsule there were a number of thin scars which showed a moderately dense lymphocytic infiltration. These scars ran parallel to the capsule for distances as great as 5 mm., but did not extend more than from 60 to 80 microns into the cortex and probably represented the atrophied cortex corticis. The cortex proper was greatly reduced in thickness, but except for the scarring just described there were no histologic differences in the right and left kidneys of this animal. There was no increase either in the number of atrophic glomeruli or of interstitial fibrous connective tissue.

Protocol 15.—In dog A 34, a female mongrel, weighing 10.8 Kg., hydronephrosis was produced for fifteen days followed by a period of repair of four hundred and sixty-five days.

May 18, 1925: The preoperative blood urea was 36.1 mg. per hundred cubic centimeters.

May 25: The right ureter was ligated.

On May 27, the blood urea was 43.2 mg.; on June 9, 43.2 mg.

June 9: The right ureter was implanted into the bladder after a period of fifteen days of complete ureteral obstruction.

On June 11, the blood urea was 35 mg.; June 15, 43 mg.; June 24, 45 mg.; July 8, 48.8 mg. (weight 10.2 Kg. and general condition excellent); July 31, 34.5 mg.; September 24, 25 mg.; October 16, 18.7 mg.; November 13, 17.5 mg.; Feb. 13, 1926, 31 mg.; March 17, 25.3 mg.; April 29, 39 mg.

September 16: The dog was killed, and a complete autopsy was not performed; only the kidneys were preserved. The right kidney was definitely smaller than the left. The greatest amount of parenchyma was found to be situated in the regions of the upper and lower poles, the central portion of the kidney suggesting an atrophic condition. The hilum was enlarged, and the ureter and pelvis were dilated. The left kidney was a normal hypertrophic organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	15.0 Gm.	45.0 Gm.
Length	6.0 cm.	6.3 cm.
Transverse diameter	2.8 cm.	4.0 cm.
Anteroposterior diameter	1.4 cm.	3.1 cm.
Cortex	2.0 mm.	6.0 mm.

The appearance of the kidneys is shown in figure 8.

Histologic Observations.—Except for the reduction in the thickness of the cortex of the left, there were no histologic differences in the two kidneys. Both were the seat of a mild chronic pyelonephritis, and the radial areas of cortical inflammation contained many atrophic glomeruli and tubules and were densely fibrosed and infiltrated by leukocytes and lymphocytes. Both kidneys showed areas in which the entire width of cortex and medulla appeared normal.

Protocol 16.—In dog A 14, a short haired, male mongrel, weighing 7.8 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of three hundred and sixty-two days.

Dec. 8, 1924, the blood urea was 28 mg. per hundred cubic centimeters.

December 11: The blood urea was 18.7 mg. The right ureter was ligated.

On December 13, the blood urea was 26.2 mg.; on December 23, 31.2 mg.

December 23: The right ureter was implanted into the bladder after a period of twelve days of complete ureteral obstruction.

On December 26, the blood urea was 33.5 mg.; Jan. 6, 1925, 27 mg.; January 13, 31.2 mg.; January 27, 26.5 mg. (weight 9.4 Kg. and general condition good); February 13, 26.7 mg.; February 26, 47 mg.; March 9, 35.1 mg.; March 16, 26 mg.; March 25, 41.6 mg.; April 1, 37.3 mg.; April 10, 25.5 mg.; April 16, 37.4 mg.; May 7, 49 mg.; June 25, 27 mg. (weight 10.8 Kg.); July 22, 23.5 mg.; October 16, 33 mg.; November 13, 40 mg.

December 20: The dog was found dead. Necropsy showed the presence of bilateral pneumonia but the other organs, excepting the kidneys, were normal. The right kidney was definitely smaller than the left, but showed grossly normal parenchyma. The right ureter was not dilated and the anastomosis between the ureter and bladder was patent. The left kidney was a normal hypertrophied organ. The urine which was obtained from the bladder showed no abnormalities. The weights and measurements of the kidneys were:

	Right	Left
Weight	14.1 Gm.	44.2 Gm.
Length	4.7 cm.	6.4 cm.
Transverse diameter	2.4 cm.	3.7 cm.
Anteroposterior diameter	1.6 cm.	3.0 cm.
Capacity of pelvis	2.0 cc.	3.0 cc.
Cortex	4.0 mm.	8.0 mm.

The appearance of the kidneys is shown in figure 8.

Pyelograms showed the right kidney and pelvis to be smaller than the left, but otherwise no definite abnormalities were seen (fig. 9).

Histologic Observations.—Except for a slight patchy pyelonephritis and the presence of serum precipitate in the glomeruli, the left kidney showed no pathologic change.

The capsule of the right kidney showed irregular thickening, and the cortex corticis had entirely disappeared. There was a wide zone of interstitial fibrosis in the outer portion of the cortex with short radial extensions at intervals toward the medulla. In this fibrosed zone the glomeruli were concentrated. The glomeruli themselves were small, fibrosed and often hyalinized, and associated with them were many atrophic contracted tubules. Deeper in the cortex proper both glomeruli and tubules appeared normal and here there was no increase in interstitial fibrous connective tissue. The medulla showed patchy areas of fibrosis. This kidney was also the seat of a very mild pyelonephritis.

Protocol 17.—In dog A 28, white male terrier, weighing 14.4 Kg., hydronephrosis was produced for twelve days followed by a period of repair of two hundred and seventeen days.

March 6, 1925: The preoperative blood urea was 50 mg. per hundred cubic centimeters. The right ureter was ligated.

On March 9, the blood urea was 60 mg.; March 13, 50 mg.; March 16, 26 mg.

March 18: The right ureter was implanted into the bladder after a period of twelve days of complete ureteral obstruction.

On March 20, the blood urea was 43.2 mg.; March 25, 36.4 mg.; April 1, 42.2 mg.; April 16, 36 mg.; June 25, 43 mg.; July 22, 48.4 mg.; September 24, 43.2 mg.; October 16, 16 mg. (general condition good).

October 21: The dog was killed.

Necropsy.—All the viscera were normal except the kidneys. The right kidney showed a firm parenchyma but was only about one-half as large as the left kidney. The right ureter was somewhat dilated as was also the extrarenal portion of the pelvis. The anastomosis between the right ureter and the bladder was patent. The left kidney was a normal hypertrophied organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	31.5 Gm.	69.2 Gm.
Length	5.3 cm.	6.6 cm.
Transverse diameter	3.3 cm.	4.4 cm.
Anteroposterior diameter	2.7 cm.	3.9 cm.
Capacity of pelvis	6.5 cc.	5.5 cc.
Cortex	4.0 mm.	8.0 mm.

The appearance of the kidneys is shown in figure 8.

Pyelograms were made of each kidney (fig. 9). These showed the right kidney to be smaller than the left with a definite dilatation of its ureter and the extrarenal portion of its pelvis, but the intrarenal portion of its pelvis appeared relatively normal. The pyelogram of the left kidney was normal.

Histologic Observations.—A few fibrosed and hyalinized glomeruli with thickened capsules were seen in the left kidney; otherwise it showed no pathologic change.

There was an irregular thickening of the capsule of the right kidney, beneath which a narrow zone of the cortex showed marked interstitial fibrosis. In this zone there was a concentration of glomeruli and tubules showing many stages of atrophy up to complete obliteration. Some of the glomeruli showed marked reduction in the size of the tufts without reduction in the size of the capsule so that there remained a large empty space between the capsule and tuft. Occasional small capsules were seen in which the tuft had entirely disappeared. There were small radial extensions of this peripheral zone of fibrosis toward the medulla. A wide inner zone of the cortex and the corticomedullary zone appeared entirely normal. There was some radial scarring of the medulla. Figure 11 shows the fibrosed peripheral zone of the cortex and the deeper unchanged zone.

Protocol 18.—In dog A 43, long haired, female mongrel, weighing 14.8 Kg., hydronephrosis was produced for thirteen days followed by a period of repair of one hundred and fifty-four days.

The preoperative blood urea was 27 mg. per hundred cubic centimeters.

June 17, 1925: The right ureter was ligated.

On June 25, the blood urea was 30 mg.; on June 30, 34 mg.

June 30: The right ureter was implanted into the bladder after a period of thirteen days of complete ureteral obstruction.

July 8: The condition of the dog was good. She weighed 14.6 Kg., and the blood urea was 30.3 mg.

On July 31, the blood urea was 24 mg.; September 24, 22 mg.; October 16, 25 mg.; November 13, 31 mg.

December 1: The dog died after an apparent illness of a few weeks.

Necropsy.—There were no external signs of injury. There was a thick purulent exudate throughout the mediastinum. The pleural cavities and lungs were not involved. The esophagus showed no perforations, nor did the trachea or large bronchi. The source of the infection was undetermined. The heart and pericardium were normal. All abdominal organs except the kidneys were normal. The right kidney was slightly smaller than the left. Its ureter and pelvis showed

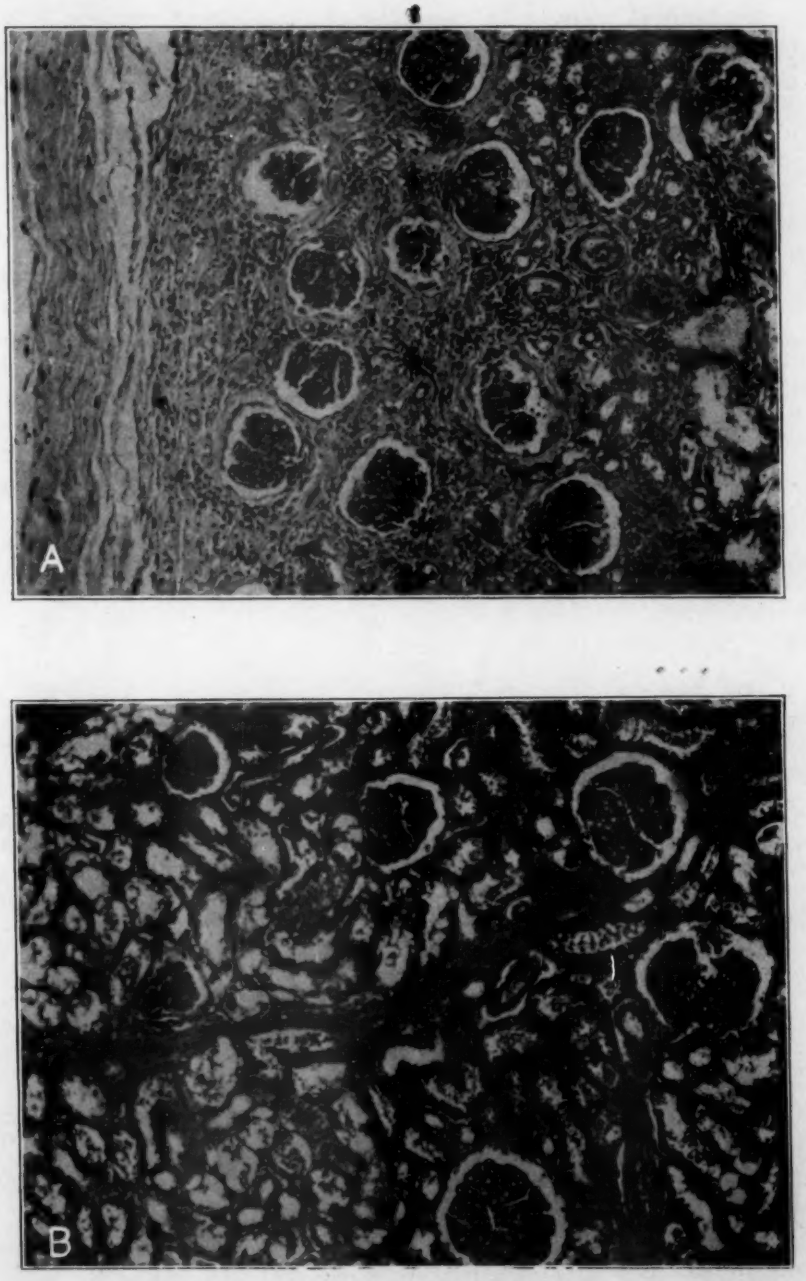

Fig. 11.—Cortex of the right kidney of dog A 28, protocol 17. The kidney had been obstructed for twelve days and allowed a repair period of two hundred seventeen days in "competition" with its undisturbed mate. *A* shows the fibrosed peripheral zone of the cortex, with atrophic tubules and concentration of glomeruli; *B*, the deeper layer of the cortex in which there was no atrophy or interstitial fibrosis; × 60.

a slight degree of dilatation, but the kidney was otherwise grossly normal. The anastomosis between the right ureter and the bladder was patent. The left kidney appeared to be normal. The weights and measurements of the kidneys were:

	Right	Left
Weight	38.1 Gm.	44.2 Gm.
Length	5.9 cm.	6.1 cm.
Transverse diameter	4.0 cm.	3.8 cm.
Anteroposterior diameter	2.2 cm.	3.0 cm.
Capacity of pelvis	5.0 cc.	5.5 cc.
Cortex	6.0 mm.	7.0 mm.

The appearance of the kidneys is shown in figure 8.

Pyelograms of both kidneys were made (fig. 9). Aside from the slight dilatation of the right ureter, no remarkable difference between the two sides was noted.

Histologic Observations.—Except for a reduction of the thickness of the cortex with radial scarring of the medulla of the left kidney, there was no histologic difference between the two kidneys of this animal.

PROTOCOL 19.—In dog A 35, a brown and white female mongrel, weighing 10.2 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of ninety-one days.

May 18, 1925: The blood urea was 29 mg. per hundred cubic centimeters.

May 20: The right ureter was ligated.

On May 25, the blood urea was 41 mg.; on June 3, 43.2 mg.

June 5: The right ureter was implanted into the bladder after a period of sixteen days of complete ureteral obstruction.

On June 8, the blood urea was 48.8 mg.; June 15, 42 mg.; June 24, 42 mg.; July 8, 27.6 mg.; July 31, 26.1 mg. The dog appeared weak and mangy, and weighed 6.8 Kg. on July 8.

September 4: The dog was killed in a fight.

Necropsy.—There was a wound in the chest which opened into the left pleural cavity and also a wound of the left lumbar region through which the left kidney had been lacerated. The dog was somewhat emaciated. The right kidney was small and firm. The anastomosis between the right ureter and the bladder was patent. There was some dilatation of the right ureter and renal pelvis. The left kidney was lacerated, but otherwise seemed to be a normal hypertrophied organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	11.8 Gm.	28.7 Gm.
Length	4.7 cm.	6.7 cm.
Transverse diameter	2.7 cm.	3.1 cm.
Anteroposterior diameter	1.5 cm.	2.4 cm.
Cortex	2.0 mm.	5.0 mm.

The appearance of the kidneys is shown in figure 8.

The pyelogram of the right kidney showed a rather small organ. The ureter and renal pelvis showed some dilatation but this was not marked.

Histologic Observations—The left kidney showed no abnormality on histologic examination.

The right kidney showed a complete disappearance of the cortex corticis with a thickened capsule. The capsular thickening was irregular and occasional prolongation of the fibrous connective tissue extended down into the underlying cortex. Only a narrow zone of the cortex adjacent to the medulla contained normal glomeruli and tubules and was comparatively free from the interstitial fibrosis

which invaded most of the cortex and medulla. Here again there was a concentration of atrophic glomeruli in the peripheral zone of the cortex. There was a mild degree of pyelonephritis.

PROTOCOL 20.—In dog A 42, a brindle male mongrel, weighing 13.6 Kg., hydronephrosis was produced for thirteen days, followed by a period of repair of seventy-eight days.

The preoperative blood urea was 18 mg. per hundred cubic centimeters.

June 17, 1925: The right ureter was ligated.

On June 25, the blood urea was 53 mg.; on June 30, 42 mg.

June 30: The right ureter was implanted into the bladder after a period of thirteen days of complete ureteral obstruction.

July 8: The blood urea was 67.6 mg., and the weight, 12.5 Kg. The general condition of the dog was good.

July 31: The blood urea was 24.9 mg.

September 16: The dog was killed.

Necropsy.—The organs were essentially normal except the kidneys. The right kidney was smaller than the left but it consisted of normal firm parenchyma. The right ureter and pelvis showed slight dilatation. The anastomosis between the right ureter and the bladder was patent. The left kidney was a normal hypertrophied organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	28.8 Gm.	38.3 Gm.
Length	5.4 cm.	6.0 cm.
Transverse diameter	2.9 cm.	3.3 cm.
Anteroposterior diameter	2.1 cm.	2.8 cm.
Capacity of pelvis	7.0 cc.	2.4 cc.
Cortex	5.0 mm.	7.0 mm.

The appearance of the kidneys is shown in figure 8.

Pyelograms of both kidneys showed a mild degree of dilatation of the right ureter and pelvis, but no other remarkable changes were noted (fig. 9).

Histologic Observations.—There was no histologic difference between the right and the left kidneys except the reduction in width of the cortex of the right kidney.

PROTOCOL 21.—In dog A 9, a mongrel poodle, weighing 8 Kg., hydronephrosis was produced for twelve days followed by a period of repair of seventy-one days.

On Nov. 13, 1924, the blood urea was 37.4 mg.; on November 14, 26.6 mg.

December 5: The right ureter was ligated.

On December 8, the blood urea was 26.1 mg.; December 11, 32.4 mg.; December 13, 46 mg.

December 17: The right ureter was implanted into the bladder after a period of twelve days of complete ureteral obstruction.

On December 23, the blood urea was 46.8 mg.; December 26, 48.5 mg.; Jan. 6, 1925, 37.4 mg.; January 13, 39.2 mg.; January 27, 35.5 mg. (weight, 5.5 Kg.); February 3, 41.6 mg.; February 13, 43 mg. (weight, 5.3 Kg.). The dog developed mange on February 13.

February 26: The blood urea was 67.4 mg. The mange was severe and the general condition was poor. The dog was killed with ether.

Necropsy.—There was some consolidation in the lower lobe of each lung. The liver, spleen, pancreas and adrenals were normal. The small intestine was found to contain a large number of worms. The right kidney was somewhat smaller than the left. The right ureter and pelvis were dilated. The parenchyma of the right kidney was firm and grossly appeared to be normal. The anastomosis

between the right ureter and the bladder was patent. The left kidney was normal. The weights and measurements of the kidneys were:

	Right	Left
Weight	16.0 Gm.	22.0 Gm.
Length	4.6 cm.	5.1 cm.
Transverse diameter	2.7 cm.	3.1 cm.
Anteroposterior diameter	1.7 cm.	2.3 cm.
Capacity of pelvis	3.0 cc.	2.5 cc.
Cortex	4.5 mm.	5.0 mm.

The appearance of the kidney is shown in figure 8.

Pyelograms were made of both kidneys (fig. 9), and aside from the slight dilatation of the right ureter and pelvis no abnormalities were seen in either pyelogram.

Histologic Observations.—There was no histologic difference between the right and left kidneys except the reduction in the cortex of the right kidney.

PROTOCOL 22.—In dog A 10, a short haired, brown female mongrel, weighing 5.5 Kg., hydronephrosis was produced for thirteen days followed by a period of fifty-six days.

The preoperative blood urea was 30 mg. per hundred cubic centimeters.

Dec. 6, 1924: The right ureter was ligated.

On December 8, the blood urea was 56.1 mg.; December 11, 50.1 mg.; December 13, 57 mg.

December 19: The right ureter was implanted into the bladder after a period of thirteen days of complete ureteral obstruction.

On December 23, the blood urea was 59.1 mg.; December 26, 56 mg.; Jan. 13, 1925, 41.6 mg.; January 27 (weight, 5.7 Kg., and general condition good); February 3, 50.6 mg.; February 13, 60.5 mg.

February 13: The dog was killed. She weighed 5.9 Kg.

Necropsy.—The organs were essentially normal except the kidneys. The right kidney was somewhat smaller than the left; the parenchyma was firm; the ureter and pelvis were slightly dilated. The anastomosis between the right ureter and the bladder was patent. The left kidney was normal and somewhat hypertrophic. The weights and measurements of the kidneys were:

	Right	Left
Weight	9.7 Gm.	15.4 Gm.
Length	3.9 cm.	4.8 cm.
Transverse diameter	2.2 cm.	2.6 cm.
Anteroposterior diameter	1.5 cm.	2.2 cm.
Capacity of pelvis	4.0 cc.	3.5 cc.
Cortex	4.0 mm.	4.0 mm.

The appearance of the kidneys is shown in figure 8.

Pyelograms were made of both kidneys (fig. 9), and these were found to be normal except for the dilatation of the right ureter.

Histologic Observations.—The left kidney showed no abnormality on histologic examination other than a mild pyelonephritis.

The right kidney showed a diffuse interstitial fibrosis most marked in the subcapsular zone of the cortex. The capsule was thickened and there was a concentration of glomeruli immediately beneath it. Some of the glomeruli appeared normal and occasional groups of normal appearing tubules extended up into the densely fibrosed cortex corticis. There was a diffuse atrophy of both tubules and glomeruli. Deeper in the cortex there were many radially disposed scars and occasional atrophic glomeruli. The medulla showed a patchy increase of fibrous connective tissue. There was a mild pyelonephritis.

PROTOCOL 23.—In dog A 46, a black and brown male mongrel, weighing 12.6 Kg., hydronephrosis was produced for nineteen days followed by a period of repair of forty-three days.

The preoperative blood urea was 36 mg. per hundred cubic centimeters.

July 1, 1925: The right ureter was ligated.

July 20: The blood urea was 44.2 mg. The right ureter was implanted into the bladder after a period of nineteen days of complete ureteral obstruction.

On July 22, the blood urea was 43.2 mg.; July 27, 53.5 mg.; August 4, 45.6 mg. (weight, 12.6 Kg.); August 13, 36.1 mg.

September 1: The dog was killed.

Necropsy.—Only the kidneys were preserved at autopsy. The right kidney was definitely smaller than the left but the parenchyma was firm and grossly appeared normal. There was a slight dilatation of the right ureter and pelvis of the right kidney. The left kidney was a normal hypertrophied organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	19.5 Gm.	41.0 Gm.
Length	5.5 cm.	6.3 cm.
Transverse diameter	2.4 cm.	3.5 cm.
Anteroposterior diameter	2.0 cm.	3.4 cm.
Cortex	5.0 mm.	7.0 mm.

The appearance of the kidneys is shown in figure 8.

Histologic Observations.—Left Kidney: No pathologic changes were noted.

In the right kidney, there was a slight diffuse increase in the interstitial fibrous connective tissue throughout the kidney. This fibrosis was most marked in the cortex corticis and the outer zone of the cortex proper. Here there were a number of fine radial scars, broadest at the capsule and extending toward the medulla. In the vicinity of the scars there was considerable atrophy of both tubules and glomeruli, many of the latter being fibrotic. In general, however, the glomerular tufts were plump and cellular. The glomeruli were smaller and approximated one another more closely than in the left kidney.

PROTOCOL 24.—In dog A 39, a brown and white female mongrel, weighing 8.6 Kg., hydronephrosis was produced for sixteen days followed by a period of repair of twenty-four days.

May 18, 1925: The blood urea was 30.5 mg. per hundred cubic centimeters.

May 20: The right ureter was ligated.

On May 25, the blood urea was 30.3 mg.; on June 3, 48.3 mg.

June 5: The right ureter was implanted after a period of sixteen days of complete ureteral obstruction.

On June 8, the blood urea was 41.6 mg.; June 15, 32 mg.; June 24, 34 mg.

June 29: The dog was killed.

Necropsy.—All the organs were normal except the kidneys. The right kidney was definitely smaller than the left and showed some dilatation of the pelvis and ureter. The parenchyma was firm. The anastomosis between the right ureter and the bladder was patent. The left kidney was a normal hypertrophied organ. The weights and measurements of the kidneys were:

	Right	Left
Weight	17.6 Gm.	40.4 Gm.
Length	5.0 cm.	6.2 cm.
Transverse diameter	2.7 cm.	4.1 cm.
Anteroposterior diameter	1.8 cm.	2.8 cm.
Cortex	3.0 mm.	6.0 mm.
Capacity of pelvis	3.5 cc.	4.0 cc.

The appearance of the kidneys is shown in figure 8.

Pyelograms were made of both kidneys (fig. 9). The right kidney appeared definitely smaller than the left and its ureter was slightly dilated, but aside from these changes the two kidneys appeared to be normal.

Histologic Observations.—The glomeruli in the left kidney were large and the tufts plump, in most instances filling their capsules. The organ was very hyperemic, many of the interlobular vessels being greatly distended.

There was marked tubular atrophy of the right kidney with degeneration of tubular epithelium. The atrophy was particularly severe in the cortex corticis and in the outer zone of the cortex proper giving this part of the kidney a compact appearance with concentration of glomeruli. There were many instances of tubular epithelial regeneration, and the regenerated tubules stood out in sharp contrast to the collapsed atrophic ones. Many of the glomeruli in the zone of the cortex had capsules of normal size but only a small portion of the tufts still intact. The greater part of such a glomerular tuft was represented by a granular basophilic mass containing a few fragmented and pyknotic nuclei lying free in the capsular space. Deeper in the cortex there were many normal appearing glomeruli, but here as well as in the medulla there were many collapsed tubules with degenerated epithelium.

In these experiments, which bear more directly on the subject of renal atrophy of disuse, the right kidney was injured by the production of a complete ureteral obstruction which existed in the various experiments from twelve to nineteen days. After the obstruction was relieved, the injured right kidney was placed "in competition" with the hypertrophic left kidney, and this period extended from twenty-four to eight hundred and seven days. According to Hinman's theory, the right kidney was thus placed at a distinct disadvantage, first because of the injury itself and secondly because its mate had become hypertrophied and accustomed to having the entire demand for renal function placed on it.

The important questions which arise concerning the fate of the right kidney are as follows: Does it undergo progressive atrophy and become a functionless and worthless organ? What are the gross and histologic changes that take place in it?

In the early part of the "competitive period" we must expect some rapid changes to occur in the right kidney. With relief of the obstruction the kidney soon changes from a large dilated structure to a considerably smaller and firmer organ. The ureter and extrarenal portion of the pelvis frequently remain permanently dilated, but the dilitation of the intrarenal portion of the pelvis may entirely disappear as in dog A 28, protocol 17 (figs. 8 and 9). In no experiment did the atrophy approach completeness and, in fact, there is no conclusive evidence that any atrophy occurred following the release of the hydronephrotic pressure. From our histlogic studies it would appear that during the period of ureteral obstruction numerous uriniferous units (tubules and glomeruli) were either destroyed or so severely damaged that necrosis

followed in spite of the removal of the obstruction. These damaged units gradually disappeared, and with their disappearance there developed considerable interstitial fibrosis, and within a period of ten or eleven weeks even the fibrous tissue had disappeared. It seems possible that this gradual but complete disappearance of these injured uriniferous units may account for the smaller relative size of the right kidney in some of those experiments in which there was a long period of repair rather than a true progressive atrophy of disuse.

The right kidney from dog A 27, protocol 13, seemed to be a functioning organ and by weight made up 36 per cent of the total renal mass even though the period of "competition" had lasted eight hundred and seven days. Both grossly and microscopically (figs. 8 and 10), this kidney consisted of tissue which was important, if not for active function, certainly as renal reserve. The excretion of phenolsulphonphthalein by this kidney was 14 per cent in 14 cc. of urine in one hour with an appearance time of eight minutes. The left kidney excreted 44 per cent of the dye in 20 cc. of urine with an appearance time of four minutes. The right kidney in dog A 41, protocol 14, constituted only 25 per cent of the total renal mass, but it had not undergone complete atrophy even though its ureter had been completely obstructed for sixteen days and the kidney had remained in "competition" with its hypertrophied mate for seven hundred and twenty-eight days. This injured kidney excreted only 10 per cent of phenolsulphonphthalein in 8 cc. of urine in one hour with an appearance time of fifteen minutes. The left kidney excreted 50 per cent of the dye in 18 cc. of urine in one hour with an appearance time of four minutes. The right kidney of dog A 34, protocol 15, also constituted only 25 per cent of the total renal mass and still showed some hydronephrosis after a repair period of four hundred and sixty-five days. The parenchyma of this organ was limited almost entirely to each pole, and grossly this kidney appeared to be more atrophic than any of the others.

If the injured kidney underwent progressive atrophy, we should expect the experiments of the longest "competitive" period to show the greatest degree of atrophy. This is not at all striking in these experiments. The percentages of the renal mass made up by the right kidneys in the experiments of longer duration are somewhat below those in the experiments of short duration, but this difference may well lie within the limits of experimental variation or may be explained by the histologic observations. Some of the experiments showed a rather surprising degree of repair rather than progressive atrophy. This was especially marked in dog A 43, protocol 18, in which after a period of thirteen days of complete ureteral obstruction and a period of repair of one hundred and fifty-four days the relative weights of the kidneys were almost the same.

The studies of the blood urea in these experiments showed no constant or definite changes. In some of the animals a temporary rise was noted after the ligation of the right ureter.

The histologic studies in this group of experiments are especially noteworthy. The left, undisturbed kidneys of these animals served as controls and in most instances were normal. One animal showed changes indicative of chronic, diffuse glomerular nephritis, while several were the seat of a pyelonephritis which was in no case severe. The glomerular tufts were in general plump and hyperemic and often there was a collection of serum precipitate within the capsules.

The right kidneys were hydronephrotic and showed changes that varied with the length of the recovery period. This variation was not absolutely uniform, some animals showing greater repair in shorter periods of time than others. In general, however, the following sequence of changes could be traced throughout the series.

The right kidney of dog A 39, protocol 24, which was obstructed for sixteen days and followed by a repair period of twenty-four days, showed changes only slightly more advanced than those observed in the right kidneys of the dogs of series I. The damage was most severe in the cortex corticis and in the outer zone of the cortex proper while the deeper zone of the cortex appeared normal (fig. 11). There was widespread degeneration of tubular epithelium with tubular atrophy and collapse. The glomeruli appeared to be concentrated in the damaged zone, and although the capsules were of normal size the tufts were exceedingly small. The decrease in the size of the glomerular tufts was not due here to a contraction but to loss of substance, and frequently a mass of necrotic cellular tissue still clung to the remnant of tuft while in other instances the capsular space was partially filled with a structureless granular basophilic mass containing a few fragmented or pyknotic nuclei. Some of the tubules were represented by a small group of degenerated epithelial cells enclosed by a basement membrane while others were lined by young regenerated epithelium containing mitotic figures. With a longer period of repair the fibrous connective tissue reaction to the injury was manifest. The cortex corticis was completely atrophic and persisted only as an irregular thickening of the capsule. There was marked interstitial fibrosis of the outer zone of the cortex proper with radial extensions of the scarring toward the medulla. There was contraction of the fibrosed zones with concentration of glomeruli many of which showed degeneration and fibrosis. Later many of the glomeruli shrank until only a small scar marked their location. The damaged tubules went on either to complete atrophy and disappearance or to epithelial regeneration and restitution. In this stage there was considerable fibrosis of the medulla and in some cases there was a proliferation of the perivascular fibrous connective tissue.

In five of the nine animals in which the period of repair was seventy days or more there was no histologic difference between the right and left kidneys except the reduction in thickness of the right cortex (fig. 10). There was no trace of the destroyed renal tissue in the right kidney of these animals. This observation was of especial interest in view of the fact that there was a definite mass reduction in the majority of the right kidneys and yet there were no signs of the atrophied structures. This would suggest that a glomerulus damaged in the course of hydronephrosis becomes atrophic and can eventually disappear without leaving any trace.

As has already been mentioned, the cortex corticis and outer zone of the cortex proper suffered the greatest damage while the deeper zone of the cortex and the corticomedullary zone appeared unchanged in recent as well as older injuries. This would seem to indicate that the distribution of the damage was associated with the vascular supply of the organ and that the arterial compression incident to the hydronephrosis affected to the greatest degree those glomeruli which were supplied by the terminal branches of the interlobular arteries and that those glomeruli whose blood supply was derived from the larger vessels closer to the arcuate arteries were not damaged by such periods of hydronephrosis as these kidneys experienced (fig. 11). Hinman and Morison [2] arrived at the same conclusion by arterial injection experiments, and stated that that portion of the kidney receiving the largest and most direct blood supply persisted longest and continued to secrete against the intrapelvic pressure.

SUMMARY AND CONCLUSIONS

Our experiments may be divided into three groups:

Group I: In these experiments the right ureter was completely obstructed for periods varying from thirteen to sixteen days, following which the animals were killed in order that the changes thus produced in the kidneys might be studied. These experiments demonstrated that such a period of ureteral obstruction caused a fairly marked degree of hydronephrosis and renal damage.

Group II: In these experiments the right ureter was completely obstructed for periods varying from eleven to nineteen days, following which the obstruction was relieved and several days later the hypertrophic left kidney was removed. In this way the entire load of renal function was placed on the injured kidney. The period of repair varied between thirty-four and eight hundred and twenty-eight days.

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2. Hinman, F., and Morison, D. M.: Experimental Hydronephrosis: Arterial Changes in Progressive Hydronephrosis of Rabbits with Complete Ureteral Obstruction, Surg. Gynec. Obst. **42**:209 (Feb.) 1926.

These experiments definitely showed that the injured kidney could undergo a remarkable degree of repair and hypertrophy if the demand were placed on it.

Group III: In these experiments the right ureter was completely obstructed for periods varying from twelve to nineteen days, following which the obstruction was relieved and the injured kidney was allowed to act in "competition" with its undisturbed and hypertrophic mate. This period of "competition" varied between twenty-four and eight hundred and seven days.

This group of experiments bears more directly on the question of renal atrophy of disuse. In no experiment did the injured kidney go on to complete atrophy even though in four of the experiments the period

TABLE 3.—*Data on Dogs with Repair of Hydronephrotic Kidney with the Hypertrophic Mate Undisturbed*

	Protocol	Duration of Complete Obstruction of Right Ureter, Days	Period of Repair of Right Kidney, Days	Weight of Kidneys, Gm.		Percentage of Total Renal Mass	
				Right	Left	Right	Left
13	(Dog A 27).....	12	807	40.5	71.5	36	64
14	(Dog A 41).....	16	728	16.2	48.7	25	75
15	(Dog A 34).....	15	465	15.0	45.0	25	75
16	(Dog A 14).....	12	362	14.1	44.2	24	76
17	(Dog A 28).....	12	217	31.5	69.2	31	69
18	(Dog A 43).....	13	154	38.1	44.2	46	54
19	(Dog A 35).....	16	91	11.8	28.7	29	71
20	(Dog A 42).....	13	78	28.8	38.3	43	57
21	(Dog A 9).....	12	71	16.0	22.0	42	58
22	(Dog A 10).....	13	56	9.7	15.4	39	61
23	(Dog A 46).....	19	43	19.5	41.0	32	68
24	(Dog A 39).....	16	21	17.6	40.4	30	70

of "competition" lasted from one to over two years. Instead of complete atrophy we found that the injured kidneys represented from one-fourth to almost one-half the total renal mass. The pyelographic studies showed that in most instances there was a return to a relatively normally shaped pelvis, although frequently the extrarenal portion of the pelvis and the ureter remained somewhat dilated.

The histologic studies, which were made in all of the experiments, may be summarized as follows:

1. The immediate effects of renal obstruction were manifested first by tubular degeneration and later by glomerular damage. Many of the glomerular tufts underwent partial or complete necrosis with subsequent disappearance of all or part of the renal unit.

2. Those kidneys which after a period of total ureteral obstruction ranging from twelve to nineteen days were allowed by relief of the obstruction to work in "competition" with their hypertrophic and undisturbed mates showed no evidence of progressive atrophy. The injured

renal elements either recovered or completely disappeared. In those experiments in which the period of repair was seventy days or more, histologic differences between injured and noninjured kidneys were not seen in five of nine animals. The other four showed varying stages of recovery.

3. Those kidneys which after a period of total ureteral obstruction ranging from eleven to nineteen days were forced to carry the entire functional load recovered rapidly, and no trace of the damaged renal units could be seen after a period of repair of forty-two days or more.

Our experiments did not demonstrate any renal atrophy of disuse and, in fact, strongly suggest that such atrophy does not occur.

In view of the experimental data presented, the theory of renal counterbalance need not be seriously considered in deciding the surgical treatment for certain renal lesions.

THE DELBET APPARATUS AND THE END-RESULTS*

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The ability to apply knowledge is a valuable possession. By this faculty, Delbet has applied the common knowledge of surface anatomy to the development of a new treatment for fractures of the leg and of the ankle. He has utilized the prominence of the malleoli and the projections of the internal tuberosity of the tibia and of the head of the fibula as points d'appui for a splint which will fix the fracture without immobilizing the knee or ankle. With good function as the goal of the treatment, Professor Delbet could not have overlooked a method of securing good reduction and solid union.

Good reduction easily secured, consolidation of the fracture stimulated, good function restored in a comparatively painless manner and the disability reduced to a minimum period without the aid of physiotherapy are the benefits I hope to demonstrate by describing again the Delbet apparatus and by reporting the end-results with this method of treatment.

DELBET APPARATUS

Materials.—1. A thin, flat board is used, which is covered on one side by zinc and to one end of which is attached a pulley at such a height that traction over it will be directly in the long axis of the bones of the leg (fig. 1, *A*). The pulley is movable laterally so that any lateral deformity can be corrected without disturbing the fracture.

2. A scultetus, or many-tailed bandage, made long enough to extend from the heel to the knee is used; the loose ends on each side are wrapped in a narrow piece of cardboard for convenience in handling.

3. Four splint forms made of crinoline are needed. Figure 2 shows in detail the measurements and the shapes of the forms. The forms are basted down the middle (the dotted line on the form in figure 2). Plaster of paris is incorporated in each layer of the crinoline as in the preparation of a plaster bandage,[1] and the forms, with their meshes filled with the dry powder, are wrapped in waxed paper and stored until occasion for use arises.

METHOD

Preliminary Procedures.—The board, zinc side up, is placed beneath the fractured limb. To prevent rotation of the fragments, the toes of the injured limb are held by an assistant. The leg is washed with soap and water, rinsed with

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* From the clinic of Dr. A. P. C. Ashhurst, Episcopal Hospital.

1. This method of the preparation of the forms differs from the directions laid down by Delbet, and the cause for the modification will be noted later in the paper.

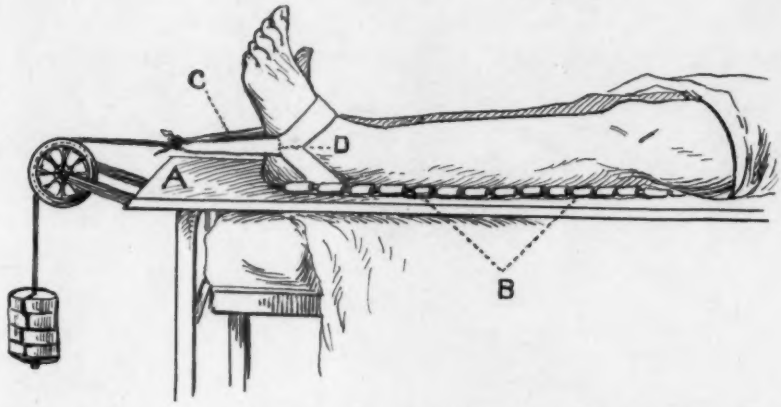

Fig. 1.—Method of applying traction: *A*, board; *B*, scultetus; *C*, traction loop, and *D*, overlapping of the flannel piece for the traction loop.

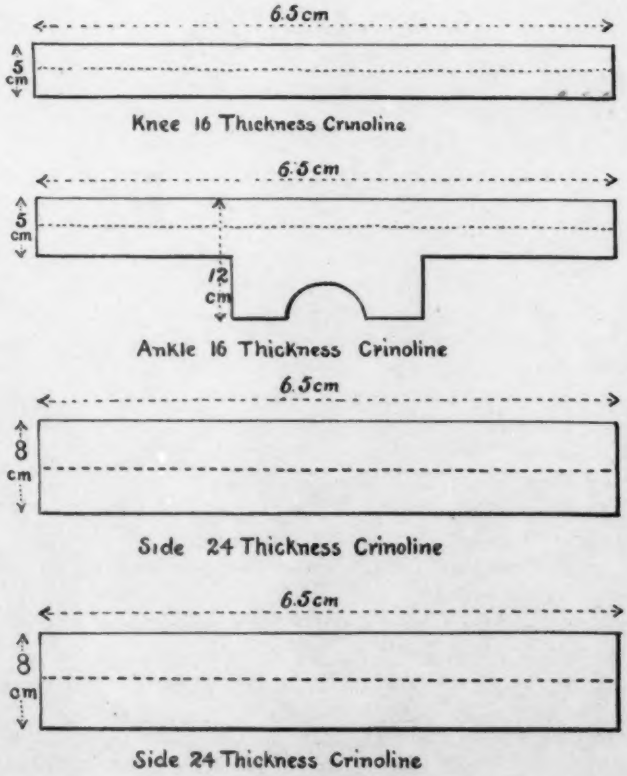

Fig. 2.—Measurements and shapes of splint forms.

alcohol and powdered; shaving is not necessary. Next, the scultetus is gently worked into position between the leg and the board (fig. 1, *B*).

Reduction.—A stirrup is made by using two strips of narrow flannel bandage (3 by 45 cm.). One strip is placed beneath the tendo achillis and above the heel. The second strip is passed over the dorsum of the foot, just distal to the ankle joint. The strips are crossed on each side below and posterior to the malleolus, and at the point of overlapping they are stitched together (fig. 1, *D*). The four loose ends (two from each strip) are carried to a suitable distance below the sole of the foot, and a loop is made by tying or stitching the ends together. To the loop (fig. 1, *C*) is attached the rope which will carry the weights.

The weights are added gradually so as to prevent spasm of the muscles. No manipulations (attempts to push fragments into place) are employed. If the preceding instructions are observed there is little pain, and no anesthetic is required. The pain ceases as soon as the weight begins to act. Repeated measurements are made to determine reduction. When reduction has been obtained, the splint is applied without disturbing the traction apparatus.

Application of the Splint.—Step 1: The ankle and the knee forms (fig. 2) are immersed in water, and when they have been saturated, they are spread out on a table and plaster of paris powder is sprinkled over both sides of each splint.

Step 2: The ankle form is placed in position by (*a*) passing one of the narrow ends through the gap which exists between the heel and the point where the calf of the leg comes into contact with the board; (*b*) gentle traction pulls through one of the wings (the area 12 cm. wide in figure 2); (*c*) the notch in the form is placed above the os calcis; (*d*) the wings are placed opposite the malleoli and the lower end carried down to within 1 cm. of the sole, and (*e*) the narrow ends and the entire form of crinoline are spread out on the board.

Step 3: The knee form (fig. 2) is passed under the knee, across the popliteal space. By seesaw motions it is moved downward to a position below the tibial tubercle, and the ends are spread out on the board.

Step 4: During steps 2 and 3, an assistant soaks the side forms by the method described in step 1. These forms are applied to the sides of the leg from the knee to within 1 cm. of the sole and then turned upward on themselves so as to provide an extra support for the subastragalar joint and the ankle joint.

Step 5: The spread out ends of the ankle piece are carried obliquely upward across the front of the leg and onto the opposite side splint. The ends must be crossed at or slightly above the point where the tendon of the tibialis anticus becomes subcutaneous. This ankle piece thus holds the lower ends of the side splints against the malleoli and the sides of the leg.

Step 6: The ends of the knee piece are carried across the front of the leg over the tibial tubercle, and serve to hold the upper ends of the side splints against the leg. Figure 3, *A* shows the splint applied and the manner of crossing of the extremities of the ankle and knee forms.

Step 7: The ends of the scultetus (fig. 1, *B*) are unwrapped from their cardboard and the strips are crossed obliquely from below upward.

Step 8: When the plaster has set firmly enough to give a clear sound on tapping with the fingers, the weights are removed and the stirrup is cut on the dorsum of the foot, and is removed entirely. The continued traction prevents displacement of the fragments during the application and setting of the splint. Traction should not be continued longer than twenty-five minutes, because of the danger of sloughs over the dorsum of the foot or on the heel.

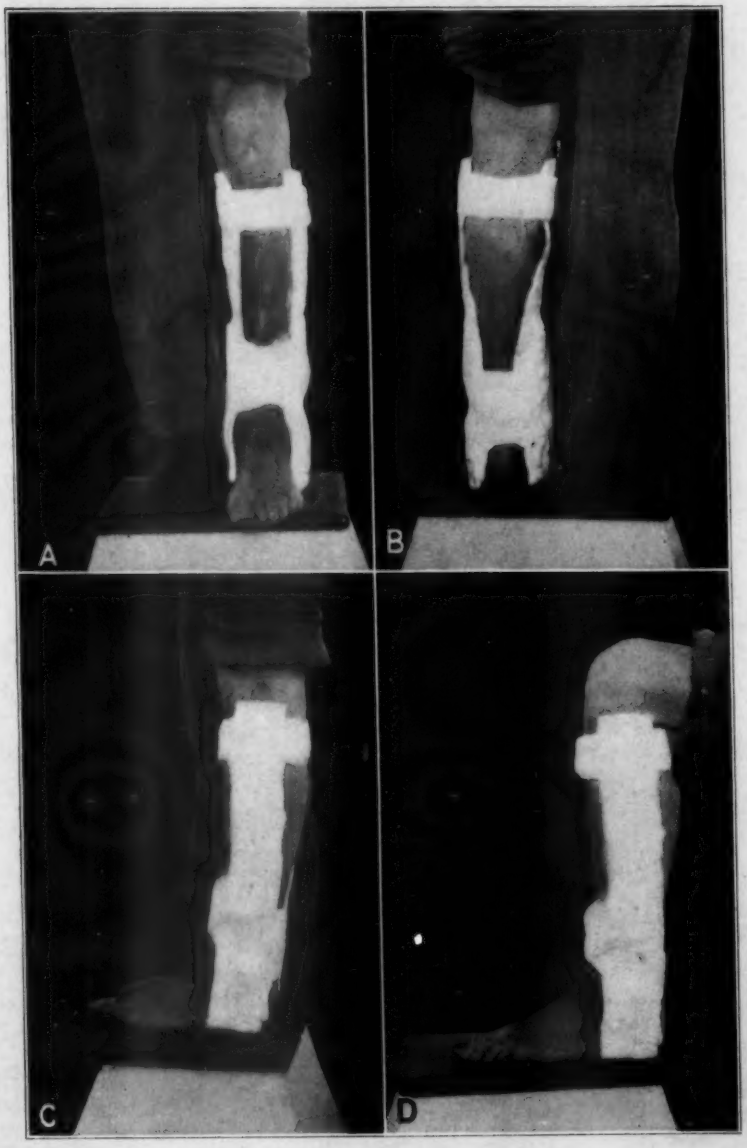

Fig. 3.—*A*, anterior aspect of splint applied. *B*, posterior aspect of same splint. *C*, lateral aspect of same splint. *D*, the flexion of the knee is not impeded by the splint.

With the aid of two assistants, the surgeon usually can apply the Delbet apparatus in from ten to twelve minutes, including the time allowed for the weight traction to overcome the deformity. Figure 3 shows the splint applied.

PRECAUTIONS

The precautions to be observed in applying the splint are as follows:

1. No attempts at manual reduction should be made during the process.

2. The knee pieces should not be carried too high because full flexion of the knee would be prevented.

3. The ankle pieces should be crossed above the point where the tibialis anticus becomes subcutaneous. If they are crossed below this point, a pressure sore will result from rubbing of the tendon against the edge of the splint when the foot is dorsiflexed.

4. The side pieces should not extend as far down as the sole.

5. Traction should not be too prolonged.

TREATMENT AFTER APPLICATION

The patient is returned to bed, the leg is elevated high (six pillows) and is surrounded by ice bags. By the strict observance of these regulations swelling can be prevented. If swelling should occur, a vicious cycle would be established resulting in troublesome ulcers.

The day following the application, the scultetus is removed, and on the same day active motions of the knee and ankle are started. Most patients are able to raise the limb from the pillows and kick it around actively the morning after the splint has been applied. In a week or ten days, the patient is removed from bed and is advised to bear weight on the injured limb with the support of crutches; at each step the patient bends the knee, bends the ankle and comes up on the toes. During the third or fourth week the crutches are discarded for a cane, and at about this time some patients, particularly children, walk without any support. The splint is removed in six weeks, and the patient returns to work as soon as confidence in the injured limb is regained. Many patients will not use the injured limb as advised, unless the surgeon takes the trouble to walk with them at first to instruct them. When they have learned, they will walk, gladly.

SUMMARY

The fracture, as all fractures should be, is reduced immediately. The reduction is by gradual traction, and the fracture is immobilized by a splint which does not interfere with motions of the knee or ankle (fig. 3). Walking encourages consolidation, because the medullary

callus is approximated in the weight-bearing.[2] Displacement of the fragments is prevented by the close application of the side splints to the bony prominence of the leg.

END-RESULTS

In the compilation of the accompanying tables, I have adhered strictly to the definitions of the Fracture Committee of the American Surgical Association:

1. The anatomic result means the position of the fragments at the time of union.

2. A bad anatomic result is one in which there is gross deformity, or shortening of more than 2 cm.

3. Moderate anatomy is a variant of the foregoing results.

4. Good anatomy indicates that there is no appreciable deformity.

5. If there are no symptoms, the result is classed as good function.

6. Pain in damp weather or swelling, limp or lessened endurance classify the result as moderate function.

7. Bad function means that the earning capacity was reduced, that a change of occupation was necessary or that there was a serious interference with the functions of the joints.

The splint was first used in the Episcopal Hospital during October, 1922. In this study are included all of the patients with fractures of the leg and of the ankle admitted to Dr. Ashhurst's service between October, 1922, and October, 1927, excluding those of 1928, because in some of the cases, the results are too recent to be classed as end-results.

During the five year period ninety-nine patients were admitted. In two of the patients the fractured leg was the less severe injury, and death occurred a few hours after admission. A third patient had an amputation of the leg for uncontrollable hemorrhage from a compound fracture. A fourth patient, not treated by the Delbet method, died from fat embolism soon after the removal of a Steinmann pin.

Seventeen of the ninety-five cases of fractures were unsuitable for the Delbet method, and twelve other patients were not treated by it; the site of the fracture and the variety of the fracture in these twenty-nine cases are shown in tables 1 and 2. At this point it should be noted that the unsuitable cases are (1) fractures above the middle third of the leg because the immobilization for such fractures should include the knee, and (2) severe compound fractures or fractures complicated by severe lacerations or abrasions, because the splint interferes with dressings; however, in these cases the splint can be used when the wounds are healed.

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2. J. F. Cowan recently showed that the separation of the medullary callus is probably the cause for nonunion (Ann. Surg. **88**:749, 1928).

Sixty-six patients, or 87 per cent of the suitable cases, were treated by the Delbet method, and if the twelve patients noted in table 2 had had this treatment, the results to be reported subsequently would have been more impressive. Fifty-three of the sixty-six patients treated by the Delbet method have been traced: one patient died of carcinoma of the stomach soon after discharge from the hospital and is excluded from the study.

TABLE 1.—*Unsuitable Cases*

	Cases
Fracture tuberosity tibia	5
Fracture of spine of the tibia	1
Severe compound fractures	4
Bad skin conditions	4
Children under 3 years	2
Fracture with pneumonia	1
Total	17

TABLE 2.—*Not Treated by Delbet Apparatus*

	Cases
Incomplete fractures	7
Children with simple fractures	4
Compound fracture (small wound)	1
Total	12

TABLE 3.—*Diagnosis in Untraced Cases* *

	Cases
Tibia and fibula, shaft	5
Shaft of tibia	4
Fibula, oblique of external malleolus (A1)	1
Ankle fracture (A2)	2
Bimalleolar fracture	1
Total	13

* Ten were over 15 years of age, three were under 15 years.

In table 3, the site and the variety of the fractures of the patients not traced are shown. Table 4 shows the variety of fractures, the site and the age incidence of the traced cases. By comparing tables 3 and 4, it will be seen that the fractures of patients not traced were not more severe than those of patients who were followed; also, the age incidence in the two groups is nearly the same. One of the untraced patients, a fat woman, who could not be induced to walk, had delayed union on discharge (refused operation), and she probably has a bad result.

In 1921, Dr. Ashhurst and I reported before the American Surgical Association [3] the end-results of a series of 100 cases of fracture of the leg and ankle in which the patients were treated in Dr. Ashhurst's clinic at the Episcopal Hospital, and in table 5 I have abstracted those results to serve as a standard for comparison with the present report. There are few compound fractures in the present series; therefore, table 5 does not include the results of any compound fractures.

TABLE 4.—*Diagnosis in Fifty-Two Traced Cases*

	Patients Under 15 Years	Patients Over 15 Years
Shaft of tibia, simple	7	2
Shaft of tibia, compound	1	0
Shaft of fibula, simple	1	2
Shaft of tibia and fibula, simple	5	11
Shaft of tibia and fibula, compound	1	0
Fibula, external malleolus (A1)	0	1
Shaft of tibia, incomplete	0	6
Tibia and fibula at ankle (A2, A3, Pott's)	0	14
Tibia and fibula at ankle, compound	0	1
Total	15	37 52 patients

TABLE 5.—*Results Reported by Ashhurst and Crossan in 1921* *

	Good, per Cent	Moderate, per Cent	Bad, per Cent
Anatomic	82	16	2
Functional	75	22	3

* The period of disability in seventy-four simple fractures of the leg and ankle was four months.

TABLE 6.—*End-Results in Patients Treated with the Delbet Apparatus*

			Functional		
	Anatomic	Good	Moderate	Bad
Good	43 (83 per cent)	40 (93 per cent)	2 (5 per cent)	1 (2 per cent)
Moderate	7 (13 per cent)	4 (57 per cent)	3 (43 per cent)	0 (.....)
Bad	2 (4 per cent)	0 (.....)	1 (50 per cent)	1 (50 per cent)
	52	44 (85 per cent)	6 (11 per cent)	2 (4 per cent)

In table 6 are recorded the results of the fifty-two traced cases. The results do not represent the work of one surgeon, nor of a specialized group; a large number of the splints have been applied by many different resident physicians and interns.

There has not been any change in the good anatomic results of the series in table 6 over the series in table 5, and this observation was to be expected because good reduction in most cases can be obtained by one means or another—skeletal traction, open reduction, etc. In this

3. Ashhurst, A. P. C., and Crossan, E. T.: Prognosis and Treatment of Fractures of Leg and Ankle: End-Results in 100 Patients, Arch. Surg. **7**:601 (Nov.) 1923.

series, however, reduction was secured in all of the cases by the closed method and without any skeletal traction, whereas, in nineteen of eighty-five cases of simple fractures, in the report of 1921, reduction was obtained by the following methods: six platings, six screw fixations at the ankle, four cases of skeletal traction (Steinmann) and two tenotomies of the tendo achillis. The present report seems to prove that reduction of a fractured leg is more easily secured by the Delbet method of traction.

Good functional results in this series (table 6) were obtained in forty-four cases, or 85 per cent, an increase of 10 per cent over those shown in table 5. In the report of 1921, 85 per cent of the patients who had good anatomy had good function as compared to 93 per cent with good function in patients with good anatomy treated with the

TABLE 7.—*Influence of Age in Cases in Which Delbet Apparatus Was Used* *

Under 15 Years		Functional		
	Anatomic	Good	Moderate	Bad
Good	14 (93 per cent)	14 (100 per cent)	(.....)	(.....)
Moderate ..	1 (7 per cent)	1 (100 per cent)	(.....)	(.....)
Bad	0 (.....)	0 (.....)	0 (.....)	0 (.....)
	15 (100 per cent)	15 (100 per cent)	0 (.....)	0 (.....)

Over 15 Years		Functional		
	Anatomic	Good	Moderate	Bad
Good	29 (79 per cent)	26 (89 per cent)	2 (7 per cent)	1 (3 per cent)
Moderate ...	6 (16 per cent)	3 (50 per cent)	3 (50 per cent)	0 (.....)
Bad	2 (5 per cent)	0 (.....)	1 (50 per cent)	1 (50 per cent)
	37 (100 per cent)	29 (79 per cent)	6 (16 per cent)	2 (5 per cent)

* In a series of eighty adults reported by Ashhurst and Crossan in 1921, anatomic results were the same, functional results were good, 65 per cent; moderate, 32 per cent, and bad, 2 per cent.

Delbet splint (table 6). It is possible that a higher percentage of good functional results in an accurately reduced fracture will be obtained by the latter method, because there are no fibrous contractures of the muscles nor of the ligaments; however, I believe that the improvements in the second report can be attributed to the absence of any operative procedure in this group. Experiences and observations have convinced me that there is a higher percentage of good functional results in fractures reduced by the closed method than in those reduced by operative procedures. In the series of operative reductions reported in 1921 (included in the results of table 5), only 73 per cent of the good reductions resulted in good function, which is 12 per cent less than the results in the group here reported (table 6). Good reduction easily secured will give the best functional results.

The termination of disability denotes the restoration of good function in most cases of fractures; therefore, the period of disability

should be a fairly accurate index of the efficacy of the method of treatment. In addition to good anatomy, good function depends on the restoration of motion in the joints bordering the fracture, on the reeducation of the muscle groups and on the establishment of an efficient venous return. Immobilization of a fracture of the leg or of the ankle by a circular cast or by a molded plaster (Stimson) splint is always followed by stiffness of the ankle, the knee or both joints, and by swelling of the leg. With the Delbet splint there is no artificial support to the venous column, there is no interference with the motions of the points (except the astragalocalcanean), and there is no hindrance to muscle action and muscle pumping on the veins; therefore, the stiff-

Fig. 4.—Swelling of left lower extremity after the removal of a circular cast.

ness mentioned, or the swelling as shown in figure 4, is rarely seen. Furthermore, with the Delbet splint, confidence in the injured limb returns at an early date because of the weight-bearing during consolidation. With good reduction, immobilization of a fractured leg or ankle by the Delbet splint should reduce the disability to a minimum period.

In a series of thirty-seven adults, the disability was shown in thirty-five.[4] The average disability of this group was three and one-half months, a reduction of one-half month, or 25 per cent, over the period

4. One of the two patients in whose cases the period of disability is unknown had an incomplete fracture of the tibia; on account of litigation, he refused to tell the period of disability. The other patient, with a fracture of the shafts of the tibula and fibula, returned to Italy.

noted in the footnote of table 5, and a reduction of nine tenths of a month over a series reported by the American Surgical Association in 1921. In only one of thirty-five cases were baking and massage used, which means that there has been a great saving of time and money. There has been an increase of 2 per cent in the bad anatomic and of 1 per cent in the bad functional results; however, the percentages in both groups are less than those reported by the American Surgical Association. The 4 per cent with bad anatomy and the 3 per cent with bad function represent three patients; one (C. G.) had bad anatomy and bad function, a second (H. B.) had bad anatomy and moderate function, and the third (R. R.) had good anatomy and bad function. Two of the bad results are directly traceable to failure of the splints to harden.

During the first eighteen months that the splint was used, soft splints were a frequent occurrence. During that period the forms were pre-

TABLE 8.—*Results Since January, 1924 (Twenty-Nine Patients Over 15 Years, Twelve Under 15 Years)* *

		Functional		
	Anatomic	Good	Moderate	Bad
Good	35 (85 per cent)	33 (94 per cent)	1 (3 per cent)	1 (3 per cent)
Moderate ..	6 (15 per cent)	3 (50 per cent)	3 (50 per cent)	0 (.....)
Bad	0 (.....)	0 (.....)	0 (.....)	0 (.....)
	41 (100 per cent)	36 (90 per cent)	4 (8 per cent)	1 (2 per cent)

* The period of disability of twenty-nine adults was two and eighty-six hundredths months (two and seventy-six hundreths months for fractures of the leg and two and ninety-four hundreths for fractures of the ankle).

pared by immersion in a creamy mixture made by adding plaster of paris to water, the method prescribed by Professor Delbet.

Early in 1924, at the suggestion of Dr. Winter, then a resident physician, Dr. Ashhurst adopted the modification noted previously in the discussion of splint forms under the heading materials. Since January, 1924, there has been only one soft splint,[5] and in this instance the plaster cream method was used.

In table 8, I have compiled the results since January, 1924. In this group there have not been any bad anatomic results and only one bad functional result. The good anatomic and the good functional results have not materially changed. The average period of disability in this group of twenty-nine adults, however, was two and nine-tenths months, a reduction of one and one-tenth months over the series of 1921. The period of disability in this group, I believe, is about the minimum that can be obtained by any method.

5. A soft splint replaced by Stimson was followed by peroneal palsy (R. R., case 2 under bad function).

In this series of fifty-two patients, there were twelve who did not obtain both good anatomy and good function. The deformities and the disabilities of the twelve patients are as follows:

Moderate Anatomy (Seven Cases).—CASE 1.—A child, aged 9 years, with a fracture of the shaft of the tibia, regained perfect function but had a slight bowing at the site of fracture.

CASE 2.—R. W., a man, aged 43, had had a fracture of the lower ends of the tibia and fibula (A3[6]) for which he had been treated in another institution for three weeks. Final examination showed bowing at the site of the tibial fracture and a shortening of 0.5 cm.; joint motions were normal, and he was free from symptoms. He returned to the same work in three months, and his wages were the same. The result was classed as good function.

CASE 3.—W. J., a man, aged 54, as a result of fractures of the lower third of the tibia and fibula, had a moderate fulness over the tibial fragment due to overriding. Shortening could not be measured, because the other leg was markedly deformed as a result of a fracture sustained eighteen years before. He returned to the same work, earned the same wages and was free from symptoms. The result was classed as good function.

CASE 4.—N. D., a woman, aged 54, had a fracture of the lower end of the tibia and of the external malleolus. Relatives reported that she had pain for two years and was disabled for one year. The final x-ray picture at the hospital showed slight posterior displacement of the lower fibular fragment. The result was classed as moderate function.

CASE 5.—S. P., a man, aged 42, had a fracture of the lower ends of the tibia and fibula (A3). At the final examination a convexity was noted over the tibial fracture without shortening. In three months he returned to the same work and earned the same wages. There was perfect function of all the joints, but because he limped slightly, the result was classed as moderate function.

CASE 6.—A. D., aged 52, had a fracture of the lower ends of the tibia and fibula (A3). On account of slight valgus the function was classed as moderate anatomy. The patient returned to work in ten weeks, but the leg swelled at the end of the day, on account of which the result was considered moderate function.

CASE 7.—J. N., aged 50, had a fracture of the middle third shafts of the tibia and fibula. The function was considered a moderate anatomic result because of convexity over the tibial fracture and a shortening of 0.5 cm. The patient returned to the same work in fifteen weeks, earned the same wages and had no symptoms, and therefore was considered as having good function.

Moderate Function (Six Cases).—CASE 1.—N. D., case 4 under moderate anatomy.

CASE 2.—S. P., case 5 under moderate anatomy.

CASE 3.—A. D., case 6 under moderate anatomy.

CASE 4.—E. C., had a Pott's or B2 fracture with good anatomy, but dorsiflexion of the ankle was limited to 90 degrees.

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6. In the case reports, A3 indicates a fracture of the lower end of the fibula plus a fracture of the whole lower end of the tibia. B2 represents a fracture of the internal malleolus plus a fracture of the fibula. A1 indicates a fracture of the lower end of the fibula only. (Ashhurst, A. P. C., and Bromer, R. S.: Classification and Mechanism of Fractures of the Leg Bones Involving the Ankle, Arch. Surg. **4**:120 [Jan.] 1922.)

CASE 5.—L. B. had a bimalleolar fracture with excellent anatomy, but had a rigid flatfoot. The patient returned to the same work in fifteen weeks.

CASE 6.—H. B., to be noted under bad anatomy.

Bad Anatomy (Two Cases).—CASE 1.—G. C., aged 32, had fractures of the lower end of the tibia and external malleolus (B2). Two Delbet splints failed to harden. Final examination three years after injury showed marked valgus. The patient had constant pain, was disabled nine months, and the earning capacity was "considerably reduced." The result also was classed under bad function.

CASE 2.—H. B., aged 54, had a fracture of the shafts of the tibia and fibula. Three Delbet splints failed to harden. The final result was a marked prominence over the tibial fracture, a shortening of the leg of 1 cm. and a limitation of flexion of the knee at 90 degrees. The patient returned to the same work in nine months and earned the same wages. The result was classed previously under moderate function.

Bad Function (Two Cases).—CASE 1.—G. C., case 1 under bad anatomy.

CASE 2.—R. R., a woman, aged 35, had an oblique fracture of the lower end of the fibula (A1). Two Delbet splints failed to harden. Stimson splints were applied and on removal a peroneal palsy was noted, which has persisted for three years.

CONCLUSIONS

Though the study of the entire five year period shows an improvement in functional results and a reduction of the period of disability, I believe that the results since January, 1924, are more representative of what can be accomplished by the Delbet apparatus. With this method, the return of function and the period of disability are dependent on the patient's persistence in the use of the injured member. Walking on the injured leg with the splint does not cause pain; it is timidity which must be overcome. Reduction of the fracture is easily secured, and there is nothing complicated about the application of the immobilizing apparatus. There are, of course, certain precautions to observe.

TRAUMA TO CENTRAL NERVOUS SYSTEM

ITS EFFECTS ON CARDIAC OUTPUT AND BLOOD PRESSURE
AN EXPERIMENTAL STUDY *

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Operations on the central nervous system are frequently accompanied by a marked diminution in the blood pressure. This decline in pressure, however, is not of as grave concern as a like drop in blood pressure during an abdominal operation. The pressure may reach a low level during an operation on the central nervous system, but if the operative procedure is stopped immediately, the pressure will usually rise without any artificial aid. In a report from the surgical clinic of Dr. Harvey Cushing, Bird [1] stated, "During operations for intracranial tumors, patients have been observed who, though their blood pressure remained too low to be recorded for from thirty minutes to three hours, recovered after spontaneously 'picking up' or following transfusion, without detectable injury to nervous tissue or other permanent ill effect." Most of these patients had lost a moderate amount of blood.

The use of the word "shock" is intentionally avoided in the title of this paper because the opinion has been expressed by several competent investigators that the syndrome usually entitled "shock" cannot be produced by injury to the central nervous system. Vincent,[2] from his experience during the war, stated that he never saw a case of shock which resulted from an injury which was limited to the central or peripheral nervous system. Mann [3] said that it was impossible to produce shock in a dog without opening the abdomen, without inducing hemorrhage or without traumatization of the medullary centers. He stated further that an animal with a very low blood pressure owing to section of the spinal cord in the lower cervical or upper thoracic region is not in a condition of surgical shock, because upon withdrawal of the anesthetic the animal will regain consciousness and respond to stimuli applied around the head. In Mann's experiments, the fall of blood

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1. Bird, C. E.: Transfusions in Acute Loss of Blood, Arch. Surg. **18**:1646 (April) 1929.

2. Vincent, C.: Contribution á l'étude de l'état de shock primitif chez les blessés de guerre, Compt. rend. Soc. de biol. **81**:887, 1918.

3. Mann, F. C.: The Peripheral Origin of Surgical Shock, Bull. Johns Hopkins Hosp. **25**:207, 1914.

pressure following section of the cord was no greater than the decrease which immediately followed section of the abdomen and exposure of the viscera. He was unable to produce shock in anesthetized animals after hours of traumatization of the great nerve trunks. Guthrie [4] and Wiggers [5] were able to produce what they considered as shock, the former by prolonged stimulation of the brachial plexus, the latter by stimulation of sensory nerves or by crushing the testes. Shock was not produced in all animals in which these methods were used. Guthrie stated, "Susceptibility varied greatly in different dogs. Some animals readily succumbed to brachial nerve stimulation alone; others only when nerve stimulation was combined with opening the abdominal cavity and visceral manipulation; while others were highly resistant under both methods."

The purpose in this paper is to record the changes observed in body temperature, pulse rate, maximum and minimum arterial blood pressures, cardiac output and consumption of oxygen produced by trauma to the cerebrum, the cervical cord and the thoracic cord.

METHOD

Dogs were used in all of the experiments. The anesthetics which were employed in different instances were morphine, chloralose and barbital. The anesthesia produced by morphine was not sufficiently profound during the stage of the operation and it was supplemented by light ether anesthesia. In most instances, the following procedure was carried out: After the animals had been narcotized for varying intervals of time, control determinations of the various factors were made. An operation was then performed which had for its object the exposure of the dura overlying the area of the central nervous system which was to be traumatized. The studies were repeated at this stage. The dura was then opened without trauma to the brain or cord, and the third series of studies were performed. The brain or cord area was then traumatized with the finger, and varying numbers of studies on the various functions were performed. The arterial blood pressure readings were obtained by placing in the femoral artery a cannula which was connected with a mercury manometer; maximum and minimum valves were used in most instances. A Benedict spirometer was employed in determining the consumption of oxygen. The connection between the animal and the spirometer was made either by the use of a tracheal cannula or by a specially constructed rubber mask which made an airtight closure over the animal's mouth. Samples of blood were withdrawn under oil and placed under oil in order to avoid contact with air. Arterial blood was obtained from the femoral artery and mixed venous blood from the right side of the heart. The analyses of the blood gases were performed with the van Slyke-Neill manometric apparatus. The output of the heart was computed by the Fick principle:

$$\frac{\text{Oxygen consumption per minute}}{\text{Arterial oxygen content minus venous oxygen content}} = \text{Number of cubic centimeters of blood flowing through the lungs per minute}$$

4. Guthrie, C. C.: Experimental Shock, J. A. M. A. **69**:1394 (Oct. 27) 1917.

5. Wiggers, C. J.: Shock and Circulatory Failure Following Trauma, Am. J. Physiol. **46**:314, 1918.

RESULTS

The effects of the operation, of the opening of the dura and of the trauma were not the same in all experiments. The observations on the effects of injury to the cerebrum, the cervical cord and the thoracic cord will be considered separately.

Trauma to the Cerebrum.—Ten experiments were performed in this group. Five of the animals were anesthetized by morphine, four by chloralose and one by ether. Ether anesthesia was unsatisfactory because of the enormous change which it caused in the output of the heart. The pulse rate increased in all experiments. The body temperature showed practically no change throughout the observations in the six experiments in which it was determined. There was little alteration in the oxygen content of the arterial blood. Usually the oxygen content of the mixed venous blood showed a progressive fall, and hence there was usually an increase in the arteriovenous difference.

There was little alteration in the consumption of oxygen in most of the experiments. On comparing the consumption of oxygen during the period shortly following the operative exposure of the dura with that of the control period, it was found to be the same in eight of ten instances, and to be slightly elevated in the remaining two. Immediately after opening the dura, the consumption of oxygen was practically the same as that in the control period in seven of ten instances and was slightly elevated in three. Varying degrees of trauma had no effect on the consumption of oxygen in six of ten instances; there was an increase in one experiment and a fall in three.

The exposure of the dura was associated with no change in the cardiac output in two of the ten experiments; there was an increase in the cardiac output in two instances and a decrease in six. When the dura was opened, the cardiac output remained the same as that for the control period in two experiments; it was elevated in one and decreased in seven. The fall usually consisted, in the main, of that which had been caused by the operative exposure of the dura, and the opening of the dura itself seemed to have little effect. Trauma to a cerebral hemisphere was associated with a fall in the output of the heart in seven of the experiments, with first a rise followed by a fall in two cases and by a sustained rise in one. A great deal of trauma was necessary in most instances to alter the cardiac output.

PROTOCOL 1: Feb. 8, 1929, weight of dog, 10 Kg.; 9 a. m., 0.081 Gm. morphine; 10:40 and 11:35 a. m., control determinations; from 11:55 to 12:15, under ether anesthesia, dura of right cerebrum exposed, not opened; 12:30, 0.049 Gm. morphine; 1 p. m., foryt-five minutes after operation, determinations; 1:30, dura opened with no ether; 1:55, twenty-five minutes after opening dura, determinations; 2:20, brain traumatized with finger for about five minutes; 2:45, twenty-five minutes after traumatizing brain, determinations; 3:15, fifty-five minutes after

traumatizing brain, determinations; 3:40, eighty minutes after trauma, determinations; 3:50, slight additional trauma; 4:05, fifteen minutes after additional trauma, determinations.

Exposure of the dura was associated with a decrease in the maximum blood pressure in six of the ten experiments and with no alteration in four. In three of the experiments there was a slight fall in the maximum pressure on opening the dura, but there was no appreciable alteration in the other instances. Trauma to the brain produced a fall in pressure in all experiments, but in several instances it had to be continued until the brain was badly macerated. Changes in blood pressure could be produced more readily by pressure at the base of the cerebral hemi-

TABLE 1.—*Result of Trauma to the Cerebrum, on Cardiac Output and Blood Pressure*

Time	Pulse Rate, per Minute	Temperature F.	Arterial Oxygen, Volumes per 100 Cc.	Venous Oxygen, Volumes per 100 Cc.	Arteriovenous Difference, Volumes per 100 Cc.	Arterial Blood Pressure		Oxygen Consumption, Cubic Centimeters per Minute	Cardiac Output per Minute Cc.
						Maximum	Minimum		
10 : 40 control	48	..	21.84	15.00	6.84	168	94	96.20	1407
11 : 35 control	54	98	22.92	16.08	6.84	170	78	84.34	1234
1 p. m. (45 min. after exposure of dura)	60	..	20.64	16.20	4.44	176	91	85.66	1929
1 : 55 (25 min. after opening dura)	88	..	20.76	14.28	6.48	159	79	110.70	1708
2 : 45 (25 min. after traumatizing brain)	124	98	19.80	13.20	6.60	132	74	89.61	1357
3 :15 (55 min. after brain trauma)	140	..	19.74	11.04	8.70	118	82	84.34	970
3 : 40 (80 min. after trauma).	175	..	19.74	9.48	10.34	98	70	73.80	714
4 : 05 (15 min. after additional trauma)	198	98	19.08	8.88	10.20	86	57	68.53	672

spheres. It was noted that pressure in some areas at the base which were not accurately localized was associated with marked temporary elevations in the blood pressure.

The minimum blood pressure was not affected by the operative exposure of the dura in four of the experiments; in three instances it was slightly elevated, and in three it fell. After opening of the dura, the pressure fell slightly in five experiments and rose slightly in three. After traumatization of the brain, the minimum pressure fell in nine of the ten experiments.

The decline in maximum blood pressure, minimum blood pressure and cardiac output usually occurred simultaneously and to approximately the same degree. Increase in pulse rate usually preceded a decrease in the functions just mentioned.

Protocols and tables 1 and 2 give the data on individual experiments.

PROTOCOL 2: March 5, 1929, weight of dog, 10 Kg.; 9:30 a. m., 0.098 Gm. morphine; 11:20, control; from 12:05 to 12:12, left cerebrum exposed, with little loss of blood; slight ether anesthesia employed; dura not opened; 1:55, 103 minutes after operation, determinations; 2:50, three minutes after opening dura, determinations; from 3:16 to 3:19, brain traumatized; 3:21, two minutes after trauma, determinations; 3:35, blood pressure had fallen a great deal; no further trauma; determinations.

Trauma to the Cervical Cord.—Six experiments of this type were performed. Morphine was used as the anesthetic in most instances. It was found in several experiments that the dura could be exposed and opened without causing any alteration in the cardiac output or in the blood pressure. Trauma to the cervical cord produced a cessation of respirations in all experiments except one. The respiratory movements

TABLE 2.—*Results of Trauma to the Cerebrum, on Cardiac Output and Blood Pressure*

Time	Pulse Rate per Minute	Temperature F.	Arterial Oxygen, Volumes per 100 Cc.	Venous Oxygen Volumes per 100 Cc.	Arteriovenous Difference, Volumes per 100 Cc.	Arterial Blood Pressure		Oxygen Consumption, Cubic Centimeters per Minute	Cardiac Output per Minute, Cc.
						Maximum	Minimum		
11:20 a. m., control.....	60	.....	19.20	13.08	6.12	140	52	85.33	1394
1:55 (103 minutes after exposure of dura).....	160	100.8	19.32	10.44	8.88	110	54	88.79	1000
2:50 (3 minutes after opening dura)	164	100.8	18.72	8.88	9.84	104	58	80.72	820
3:21 (2 minutes after trauma to brain	200	100.9	19.20	6.00	13.20	98	58	80.72	612
3:35 (16 minutues after trauma to brain.....	200	101.0	18.60	3.00	15.60	37	20	53.04	340

would first become slow and then shortly stop entirely. An effort toward respiration, however, was being made by the accessory respiratory muscles, as was evidenced by movements of some of the muscles of the neck and face. The pulse became very slow and remained strong for a long period, during which tracheal insufflation was instituted.

In the one experiment in which trauma to the cervical cord did not produce immediate death, several series of determinations were made. The cardiac output was not determined before the dura was exposed, but this procedure caused no alteration in the arterial pressure. The cardiac output, the maximum blood pressure, the minimum blood pressure and the mean blood pressure declined together. The decrease in cardiac output was associated with practically no alteration in the oxygen consumption and with an increase in the arteriovenous difference in oxygen content. The results of this experiment are given in table 3.

PROTOCOL 3: Jan. 15, 1929, weight of dog, 9 Kg.; 11 a. m., 0.098 Gm. morphine; 11:30, blood pressure 120 systolic, 80 diastolic; from 11:45 to 12:15, spinal cord

in midcervical region exposed for about 3 cm., with a small loss of blood; ether anesthesia; dura not opened; 1:45, ninety minutes after exposure of dura, determinations; 2:15, dura opened; cord not traumatized; 2:20, five minutes after opening dura, determinations; 2:40, twenty-five minutes after opening dura, determinations; from 3:14 to 3:18, cord traumatized with finger; 3:26, eight minutes after trauma ended, determinations; 3:52, thirty-four minutes after trauma to cord, determinations.

Trauma to the Thoracic Cord.—Three experiments of this type were performed. Morphine was used as a narcotic. Usually the dura was exposed and opened without any fall in the arterial blood pressure or in the cardiac output. A great deal of trauma was necessary to produce a definite decrease in either the blood pressure or the output of the

TABLE 3.—*Results of Trauma to the Cervical Cord, on Cardiac Output and Blood Pressure*

Time	Pulse Rate per Minute	Temperature F.	Arterial Oxygen, Volumes per 100 Cc.	Venous Oxygen, Volumes per 100 Cc.	Arteriovenous Difference, Volumes per 100 Cc.	Arterial Blood Pressure		Oxygen Consumption, Cubic Centimeters per Minute	Cardiac Output per Minute, Cc.
						Maximum	Minimum		
1:45 p. m. (90 minutes after exposure of dura)	98	96.0	19.44	15.00	4.44	124	80	52.71	1187
2:20 (5 minutes after opening dura)	96	....	19.92	14.28	5.64	110	78	60.62	1075
2:40 (25 minutes after opening dura)	100	94.1	18.84	13.68	5.16	88	78	52.71	1021
3:26 (8 minutes after trauma to cord)	150	....	18.60	12.24	6.36	64	58	55.35	870
3:52 (34 minutes after trauma to cord)	150	93.8	18.84	11.04	7.80	66	54	47.44	608

heart. When an alteration of this kind was produced, the blood pressure and cardiac output fell together. There was little alteration in the consumption of oxygen. The results of an experiment are recorded in table 4.

PROTOCOL 4: Jan. 1, 1929, weight of dog, 12 Kg.; 9 a. m., 0.098 Gm. morphine; 10:50, control determinations; 12:10, ten minutes after completion of operation for exposure of cord in lower thoracic region; light ether anesthesia, dog awakening at time of observations; practically no loss of blood; dura not opened; 2:45, dura opened for a distance of 3 cm.; dog completely quiet; 2:50, determinations, five minutes after opening dura; 3:15, determinations, thirty-five minutes after opening dura; from 4:05 to 4:08, slight trauma to cord with a blunt instrument; cord not crushed; 4:12, four minutes after trauma, determinations; 4:47, thirty-nine minutes after trauma to cord, determinations; 5:15, sixty-seven minutes after trauma to cord, determinations; 5:30, cord crushed by clamp for distance of about 2.5 cm.; animal struggled little; 5:50, determinations, twenty minutes after crushing cord; 7:15 pulse 188; blood pressure 80 systolic and 64 diastolic.

COMMENT

The data presented here throw some light on the question as to whether or not shock can be produced by trauma to the central nervous system. The operation, the production of the trauma and the collection of the samples of blood for gas analyses resulted in the loss of a moderate amount of blood. The simple removal of the same amount of blood from an animal that did not have the operation and the trauma would not produce changes of the magnitude reported in this paper. The amount of blood lost is comparable to that lost in operations on the central nervous system.

TABLE 4.—*Results of Trauma to the Thoracic Cord, on the Cardiac Output and Blood Pressure*

Time	Pulse Rate per Minute	Temperature F.	Arterial Oxygen, Volumes per 100 Cc.	Venous Oxygen, Volumes per 100 Cc.	Arteriovenous difference, Volumes per 100 Cc.	Arterial Blood Pressure		Oxygen Consumption, Cubic Centimeters per Minute	Cardiac Output per Minute, Cc.
						Maximum	Minimum		
10 : 50 a. m., control	60	96.8	17.88	13.56	4.32	128	66	75.64	1751
12 : 10 (10 minutes after exposure of cord)	65	96.0	17.40	13.92	3.58	126	68	76.00	2151
2 p. m. (1 hour 50 minutes postoperative)	50	95.8	17.52	13.80	3.72	124	70	84.87	2281
2 : 45 p.m. (5 minutes after opening dura)	110	....	18.12	13.44	4.68	126	74	95.94	2050
3 : 15 (35 minutes after opening dura)	85	....	17.28	12.24	5.04	118	64	92.25	1830
4 : 12 (4 minutes after trauma to cord)	67	....	17.64	14.28	3.46	122	70	95.94	2772
4 : 47 (39 minutes after trauma to cord)	160	95.6	17.64	9.60	8.04	98	76	81.18	1009
5 : 15 (67 minutes after trauma to cord)	158	....	17.52	10.44	7.08	92	68	70.11	990
5 : 50 (20 minutes after crushing cord)	175	....	17.52	8.64	8.88	96	70	73.80	831

Wiggers [6] studied shock that was produced by manipulation of the intestines, by trauma to the sciatic nerve and testicle and by hemorrhage; he found that the changes in the circulatory mechanism were essentially the same. Blalock,[7] in a study of the effects of hemorrhage, found that the changes in cardiac output preceded alterations in the mean blood pressure. Usually the maximum pressure fell and the minimum pressure rose before there was a marked reduction in the output of the heart. In the present study, there was a rise in both systolic and diastolic blood pressure, which in some instances occurred immediately after the

6. Wiggers, C. J. (footnote 5); Shock: Abdominal, Initial and Progressive Stages of Circulatory Failure in Abdominal Shock, Am. J. Physiol. **45**:485, 1918; Differentiation Between Circulatory Failure due to Shock and Other Causes, J. A. M. A. **70**:508 (Feb. 23) 1918.

7. Blalock, Alfred: Mechanism and Treatment of Experimental Shock: I. Shock Following Hemorrhage, Arch. Surg. **15**:762 (Nov.) 1927.

trauma and lasted for a few seconds. The cardiac output could not be determined in such a short interval by the method used. After this brief initial period, in a few experiments and in all other instances, it was found that the cardiac output and the maximum and minimum blood pressure declined together. These changes were usually preceded by a definite quickening of the pulse. This is in contrast to the observation in shock produced by hemorrhage. The first change in hemorrhage, with the exception of a lowering of the volume of blood, was a vasoconstriction which caused an increase in the minimum blood pressure. These facts are evidence that vasoconstriction does not occur after injury to the central nervous system. It is also significant that the cardiac output falls tremendously after hemorrhage before the mean blood pressure falls, whereas no instance of a definite fall in cardiac output was found in these experiments with trauma without some fall in the blood pressure. In other words, after trauma to the central nervous system, there is not the critical level in the blood pressure which seems to exist in hemorrhage. This observation probably accounts for the fact that a fall in blood pressure is not as serious during operative procedures on the central nervous system as it is during or after other types of operations or after hemorrhage.

As has been stated previously, the effects of the loss of small amounts of blood cannot be ruled out in these experiments, but the fact that the changes here reported are different from those produced by hemorrhage alone indicates that hemorrhage is not the causative factor. We believe that the results obtained are the results of the trauma to the central nervous system. The rise in the minimum arterial pressure and the fall in the maximum pressure in uncomplicated hemorrhage which results in a lessening of the pulse pressure denotes the onset of a grave condition. The pulse pressure usually maintains a high level during the early stages of trauma to the nervous system, and this is probably a good prognostic sign.

In hemorrhage the blood pressure is not of paramount value as an indication of incipient shock. The blood pressure serves as a more accurate index of the condition of the circulation after trauma to the central nervous system because alterations in the blood pressure parallel other circulatory changes.

The increase in diastolic pressure after uncomplicated hemorrhage in moderate amounts is due to a contraction of the arteries in an effort to keep the arterial blood pressure at the normal level. Undoubtedly there is a different mechanism which operates after trauma to the central nervous system. It is likely that the injury causes a relaxation of the vessels of some large area, such as the splanchnic region, or perhaps of the entire body. The decline in pressure may appear quite early and

probably is not due to the accumulation of toxic products that cause capillary dilatation and increased permeability.

A decline in the blood pressure and cardiac output was found in most instances without any decrease in body temperature. This may be explained in part by the fact that dogs have sweat glands which allow for the dissipation of heat.

Trauma to the nervous system in dogs, accompanied by a decline in the arterial blood pressure and the output of the heart, may or may not be associated with a decrease in the total consumption of oxygen. Henderson, Prince and Haggard [8] stated that metabolism is lowered in animals in which experimental shock is produced. Aub,[9] working on cats, produced shock by trauma to the leg in some instances and by hemorrhage alone in others. He stated: "Experimental traumatic shock causes a marked fall in the rate of basal metabolism to 70 per cent of the original level. The degree of fall is dependent on the severity of the shock produced. The effect of hemorrhage is not constant. It may temporarily lower, or have no immediate effect on the metabolic rate." The observations after hemorrhage were confirmed by Blalock.[7] Cannon [10] emphasized the importance of maintaining the delivery of oxygen to the tissues and stated that most of the harm which results from the low arterial pressure and diminished volume of blood is due to the poor supply of oxygen to the tissues. It is interesting to note in these experiments that the total consumption of oxygen in several instances remained at the normal level, while the blood pressure, the output of the heart and the volume of blood were diminished. Even in instances such as those reported by Aub, in which the basal metabolism fell 30 per cent, the decline can be accounted for partially by decrease in blood flow in the "less essential organs." Gesell [11] studied the blood flow through the salivary gland after hemorrhage and injury to the tissues and found striking decreases in the flow. In one experiment, for example, he found that the removal of 10 per cent of the estimated volume of blood caused a decrease of 60 per cent in the flow of blood through the salivary gland. It is likely that a similar condition exists in the extremities.

The volume of the circulatory blood is certainly reduced in shock produced by all methods. Shock may be found with a normal arterial

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8. Henderson, Y.; Prince, A. L., and Haggard, H. W.: Observations on Surgical Shock: A Preliminary Note, J. A. M. A. **69**:966 (Sept. 22) 1917.

9. Aub, J. C.: Studies in Experimental Traumatic Shock: I. The Basal Metabolism, Am. J. Physiol. **54**:388, 1920.

10. Cannon, W. B.: Traumatic Shock, New York, D. Appleton & Company, 1923.

11. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and Tissue; Abuse in Relation to Secondary Shock, Am. J. Physiol. **47**:468, 1918.

blood pressure, normal consumption of oxygen, normal pulse rate and a normal temperature. It almost certainly cannot be produced by any method which does not cause a lowering of the cardiac output and of the oxygen content of the mixed venous blood. It is believed that this work emphasizes the futility of trying to designate by the word shock or any other term the varying conditions which result after trauma and hemorrhage. A similar mistake would be the consideration of all fevers as of one type.

SUMMARY

The effects on the pulse rate, temperature, maximum and minimum arterial blood pressures, arterial and venous oxygen content, consumption of oxygen and cardiac output were studied after (1) the operative procedure that was necessary for the exposure of the dura, (2) the opening of the dura, and (3) trauma to the central nervous system in the (*a*) cerebrum, (*b*) cervical cord and (*c*) thoracic cord.

1. In some instances the operation that was necessary for the exposure of the dura and the opening of the dura caused no decrease in the arterial blood pressure or in the cardiac output.

2. Trauma to the central nervous system caused a diminution of the maximum and minimum arterial pressure and the cardiac output.

3. The pulse rate usually increased before the blood pressure and cardiac output altered.

4. The blood pressure and the cardiac output apparently changed simultaneously.

5. The alterations in the consumption of oxygen were variable, but in the majority of instances, trauma caused no appreciable alteration from that of the control period.

6. In the majority of instances, changes in body temperature were negligible.

7. The differences in the effects of hemorrhage and trauma to the central nervous system have been stated.

THROMBO-ANGIITIS OBLITERANS

GENERAL DISTRIBUTION OF THE DISEASE *

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Von Winiwarter,[1] in 1878, described a case in which the arteries of a lower extremity were occluded by a chronic proliferative process arising from the intima and showed an inflammatory reaction of the walls of the vessels. He called this lesion "endarteritis obliterans."

Since then many writers have described this disease, but it was not until the studies of Buerger [2] in 1908 that the pathologic changes were minutely described and the disease established as a definite clinical and pathologic entity. From the time of the first description by von Winiwarter [1] to the present, there has been a tremendous amount of study and investigation of this lesion.

It is the object in this paper to direct attention to the more general distribution of the disease in contradistiction to what has previously been believed concerning it—that it is a disease involving the blood vessels of the extremities exclusively. It attacks the walls of the blood vessels, both veins and arteries, throughout the entire vascular system, the cranial, thoracic and abdominal vessels as well as the vessels of the extremities. The signs and symptoms are characteristic of the vessels involved, so that the lesion affecting the arteries of the brain may give rise to a hemiplegia, of varying degree of severity, or, should the coronary vessels be involved, the characteristic symptoms of coronary thrombosis or angina pectoris may ensue.

This study is based on thirty-four cases. Twenty-seven were observed by us, including two of hemiplegia in which a definite diagnosis of thrombo-angiitis obliterans had been made and one case of coronary thrombosis in the presence of progressive thrombo-angiitis obliterans. Seven cases were collected from the literature. We have intentionally

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1. Von Winiwarter, Felix: Ueber eine eigentümliche Form von Endarteritis und Endophlebitis mit Gangrän des Füsses, Arch. f. klin. Chir. **23**:202, 1878.

2. Buerger, Leo: Thrombo-Angiitis Obliterans: A Study of the Vascular Lesions Leading to Pre-Senile Spontaneous Gangrene, Am. J. M. Sc. **136**:567, 1908.

eliminated cases that showed gross arteriosclerotic changes in the vessels to which occlusion of the lumen could be attributed. The patients whose cases we report were under the age of 50 and had shown definite evidence of thrombo-angiitis obliterans for many years. We report these cases because they show a general distribution of the disease. We feel that this is not a large series on which to base conclusions, but we hope that this paper may stimulate further interest and observation.

REPORT OF CASES

CASE 1.—J. S., a Jew, aged 48, born in Russia, was operated on for a doudenal ulcer in 1918 when a gastro-enterostomy was done. His symptoms, however, were not relieved, and six months later he was operated on again. Shortly upon leaving the hospital after the second operation, he began to complain of severe pain in the right calf on walking and more or less constant pain and numbness in the toes of the right foot. In 1921, gangrene developed in the third toe of the right foot. He remained in a hospital in Boston for eleven weeks, when his toe was amputated. The pain in his right leg and foot, however, continued, and shortly afterward gangrene developed in the second toe. At this time, the patient entered the Beth Israel Hospital, where a diagnosis of thrombo-angiitis obliterans was made. An amputation below the knee was done. The stump seemed to heal well and the patient was sent home. Two months later, he came back to the hospital complaining of bleeding hemorrhoids. These bled profusely and produced a severe secondary anemia, which required a transfusion. The hemorrhoids were removed under local anesthesia. At this time, he began to complain of some pain, not severe, in the left calf. Pulsation in the left dorsalis pedis artery was not felt.

The patient got along well with an artificial right limb until June, 1928; then he came back to the hospital because he was unable to raise the stump of his right leg and his speech was slow and thick. On admission to the hospital, he was found to be suffering from a hemiparesis of the right side, involving the right leg and arm and also the right side of the face. The right knee jerk was exaggerated. The abdominal reflexes were abolished. The cremasteric reflex on the right could not be obtained. The blood pressure was 116 systolic and 60 diastolic. The Wassermann reaction of the blood was negative; that of the spinal fluid was negative. His heart was not enlarged. A systolic murmur was heard over the precordia. The aortic second sound was not accentuated.

The paralysis of the right side cleared rapidly. In three weeks, the patient was out of bed and got along pretty well with the support of one crutch. About six weeks after admission, he was discharged from the hospital with a slight residual paralysis.

During his stay in the hospital, the patient had considerable trouble with his left lower extremity, for which he was given sodium citrate. It may be of interest to note a decrease in the pain in the left calf after daily intravenous injections of 20 cc. of a 20 per cent solution of sodium citrate. Another fact of interest is that this patient was not a cigaret smoker; all he ever smoked was three small cigars daily.

Comment.—This patient had a number of vascular accidents. While it is true that a patient suffering from thrombo-angiitis obliterans may have duodenal ulcer, bleeding piles and cerebral thrombosis, the question arises whether all these vascular accidents might not be due to one underlying condition.

In the absence of arteriosclerosis, cardiorenal disease or hypertension, it may be reasonable to suppose that there is a relation between the thrombo-angiitis obliterans of the lower extremities, the presence of which was definitely proved, and the other vascular accidents, and that they are all of the same pathology.

That the disease at the time of writing had not yet become quiescent is shown by the fact that the patient still had intermittent claudication in the left leg and a certain amount of edema and the usual cyanosis of the left foot.

CASE 2.—M. G., a Jew, aged 45, born in Russia, had complained for about a year and a half of pain in both calves on walking, more marked in the right, and extremely severe in the right foot, particularly in the great toe. Examination at the time the pain was first noted showed no pulsation in the dorsalis pedis artery on the right, but it was definitely felt in that on the left. There was a great deal of redness and tenderness of the right toe. The patient was at another hospital for twelve weeks, where a diagnosis of thrombo-angiitis obliterans was made. The pains in his foot were most excruciating, and did not respond to any kind of treatment that was tried, including inoculation with typhoid vaccine. An ulceration of the great toe then began to develop, and an amputation of the leg was considered; however, a ganglionectomy and ramisection were performed, the second, third and fourth right lumbar sympathetic ganglions being removed. The pain stopped immediately, and the ulceration of the toe healed completely. He was discharged from the hospital feeling perfectly well; the pulsation in the dorsalis pedis artery on the right, however, could not be felt.

A few months after he left the hospital, a superficial phlebitis of the right leg developed, which subsided with moderate rest. He soon resumed his work as salesman. While in the West, one day early in August, 1928, he suddenly felt a tingling in his left arm and left leg, which lasted a few minutes. About three quarters of an hour later, he completely lost the power of his left arm and left leg and fell. He was placed on a train and sent on to his home in Boston. He was seen within twenty-four hours after the onset of his trouble. At this time, he had a complete paralysis of the left arm and left leg with a slight involvement of the left side of the face.

Examination.—The physical examination on his entrance to the Beth Israel Hospital on Aug. 10, 1928, showed complete paralysis of the left arm and left leg. Pulsations in the dorsalis pedis artery on the right were not felt, but were felt in that on the left. All the reflexes on the left were exaggerated. A positive Hoffmann's sign was elicited on the left. There was clonus of the left ankle, but no Babinski sign. Abdominal reflexes were active on both sides. There were no sensory disturbances. Examination of the fundus showed considerable tortuosity of the veins, which were rather dark, and the arteries showed a white line around the border. The results of the physical examination were otherwise negative. The heart was not enlarged; the sounds were of good quality without murmurs. The blood pressure was 110 systolic and 80 diastolic. There was no evidence of any renal disease. The Wassermann reaction of the blood was negative. An x-ray picture of the lower extremities showed "no deviation from the normal in the bones and articular surfaces," and "evidence of calcium deposits on the blood vessels around the ankle joints."

The patient felt well and recovered from the paralysis with extraordinary rapidity. A few days after his entrance to the hospital, he had obtained motion in the arm and the leg, and two weeks after entrance he was able to walk.

On August 30, the patient began to complain of pain in the right leg. Examination revealed a superficial phlebitis, characteristic of thrombo-angiitis obliterans, the so-called migrating phlebitis. About four weeks after his admission, the patient was walking, and the grip of his left arm was almost equal to that of the right.

Comment.—This man showed no clinical evidence of arteriosclerosis or cardiorenal disease; he had thrombo-angiitis obliterans with two attacks of superficial phlebitis. A complete hemiplegia developed, which cleared up within so short a time that it could not well have been due to a cerebral hemorrhage. It is interesting to note that the ganglionectomy certainly relieved his symptoms, but apparently did not stop the progress of the disease, as is evidenced by the subsequent history of phlebitis.

The condition at least suggests that the vascular lesion of the brain was similar in character to that of the vascular disease in the legs and that the hemiplegia was probably due to partial occlusion, with vascular spasm of the cerebral arteries, rather than to cerebral hemorrhage.

The fact that the x-ray picture showed evidence of a deposit of calcium in the blood vessels about the ankles is no indication that the occlusion of the blood vessels was the result of arteriosclerosis.[3] It simply meant that he was approaching the age when arteriosclerotic changes begin to manifest themselves; it had nothing to do with the disease in question.

Case 3.—J. M., a Jew, aged 46, married, born in Russia, was referred to the Beth Israel Hospital on Nov. 17, 1928, by Dr. S. A. Levine. Ten years before, the patient had had cramps in the calves when walking. This was diagnosed by Buerger as thrombo-angiitis obliterans. The condition gradually became worse; gangrene of the first two toes of the left foot set in, and one and one-half years before his admission to the Beth Israel Hospital an amputation of both toes was performed. During the few months preceding his admission, the pain in the right leg and right foot became much worse, and a marked change took place in the color of the dorsum of his foot. It was cherry red. Four weeks previous to admission, while in bed, he was suddenly taken with an agonizing pain in the chest of a constricting character, which lasted for thirty-six hours. After this, he had shortness of breath, which he had never experienced previously. On more careful questioning, it was found that for two months previous to the attack mentioned he had had similar minor pains in his chest, which were of short duration. His blood pressure, which varied from 130 to 140 systolic ordinarily, fell to 90 during the attack. Pain was entirely gone when he was last under observation, but he complained of dyspnea, especially at night. When first seen by Dr. Levine, the patient looked sick and dyspneic. His heart was considerably enlarged,

3. Brown, G. E., and Henderson, M. S.: Diagnosis and Treatment of Arterial Vascular Diseases of the Extremities, J. Bone & Joint Surg. **9**:613 (Oct.) 1927.

and there was a definite sound of pericardial friction and some evidence of congestive failure. The patient when last seen complained of severe pain in the right foot, more particularly in the right great toe.

His other past history and the family history were negative. His wife and three children were living and well.

Examination.—The patient weighed 117 pounds (53.1 Kg.). The vital capacity of his lungs was 1,700 cc. (markedly diminished from normal). The urinalysis was negative. The blood pressure was systolic, 108; diastolic, 70. The Wassermann reaction of the blood was negative. The pupils were equal and reacted normally. The patient looked sick and dyspneic. There was no glandular enlargement. The throat was normal. The lungs showed a moderate number of moist râles at both bases; breath sounds were diminished. The heart was considerably enlarged; the measurements were 13 cm. to the left and 5 cm. to the right. There was a definite fading sound of pericardial friction over the precordia. No endocardial murmurs were heard. There was a question of gallop rhythm. No peripheral edema was observable over the shins or sacrum. No pulsations could be felt in any of the main vessels throughout both lower extremities. The first two toes of the left foot had been amputated. The dorsum of the right foot was cherry red to purple, and the toes felt cold. The radial and ulnar pulses in the upper extremities could be felt. Electrocardiographic tracings showed certain minor changes in the T-wave in lead 1 which are frequently seen in cases of coronary thrombosis. This patient had a ligation of the right popliteal vein. During the operation, the femoral artery as far as it could be felt, showed no evidence of pulsation, nor could pulsation be felt in the popliteal artery.

Comment.—This patient had had thrombo-angiitis obliterans for many years. About ten weeks previous to our study of his case early symptoms of angina pectoris developed. Four weeks previously, he definitely had an attack of coronary thrombosis. The severe pain, the preceding angina pectoris, the fall in blood pressure, the development of dyspnea, the finding of pericardial friction and the change in the electrocardiograms made this diagnosis certain. The right leg, however, when he was last seen, was becoming more painful. The case is interesting especially in that the same condition and the same sequence developed in the coronary arteries that probably were taking place in the arteries of the legs, first the intermittent spasm and finally a closure.

CASE 4 (Riesman[4]).—M. A., a married man, aged 44, a Russian manufacturer, for several years had had a good deal of pain in the epigastrium, for which he had consulted physicians and received various diagnoses, such as duodenal ulcer and that of gallstones. One day Dr. Riesman was asked to see him and found him in an attack characterized by excruciating pain in the epigastrium and profound shock, ending in eventual unconsciousness. The symptoms and physical signs were those of coronary occlusion. The patient died during the attack. On going over his records, Dr. Riesman found that the man had come to him on one occasion several years before, complaining of sciatica. On examination, he found the pulse of the dorsalis pedis artery absent and after close study was able to make a diagnosis of intermittent claudication.

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4. Riesman, David: Myocardial Disease and Its Gastric Masquerades, J. A. M. A. **91**:1521 (Nov. 17) 1928 (case 3).

Comment.—It was justly assumed that the intermittent attacks of abdominal pain that had led to a diagnosis of gallstones or ulcer had been due to a temporary or permanent occlusion of small branches of the coronary artery; the possibility of a true abdominal angina, an intermittent claudication of branches of the celiac axis, has also to be kept in mind.

CASE 5 (Czerna[5]).—A Polish Jew, aged 36, since the age of 20, had had recurring attacks of pain in the legs, which confined him to bed for from four to six weeks at a time. There were intervals of several years when he was free from pain. He also, at one time, had an "acute attack of heart trouble" for which he remained in bed for four weeks. At one time, paralysis developed in the right side of the face, and lasted for four weeks; at the onset of this attack he also had some difficulty with his speech. At another time, he had an attack of unconsciousness, which was diagnosed as due to a cerebral embolus. The present attack started one year before, when he suddenly began to have severe pain in the left foot and left leg. About three months before his entrance to the hospital, he had an ulcer over the right internal malleolus. A few weeks previous to admittance, he also had an attack of pain in the left arm and hand, which lasted for three weeks.

Examination.—The muscles of the right thigh and the lower part of the right leg were atrophied. Over the right internal malleolus, he had an ulcer about 1 cm. in diameter. There was no edema. The veins were markedly dilated and tortuous. Pulsation in the dorsalis pedis artery and the posterior tibials, on both sides, could not be felt, and there was no pulsation in the right femoral artery. Pulsation in the left radial artery could be felt about 5 cm. proximal to the styloid process; beyond that the artery was felt as a fibrous cord. The heart was slightly enlarged. There were no murmurs. Blood pressure was 130 systolic and 90 diastolic. The urine disclosed nothing abnormal and the Wassermann reaction of the blood was negative. He showed signs of left facial paralysis. His left knee jerk was more lively than the right. There were no sensory disturbances. He remained in the hospital for eight months. After leaving the hospital, he had an attack of severe pain in both feet, and six days later, after the pain had somewhat subsided, he became unconscious, had convulsive seizures and died.

On postmortem examination, it was found that his heart was slightly enlarged and weighed 400 Gm. The wall of the left ventricle was hypertrophied. There were some yellowish-white spots on the left auricle. On the aorta, near the origin of the coronaries, there were a few grayish-white, rough spots. The ascending branch of the left coronary, 3 cm. from the orifice, was occluded by fibrous tissue. Near the orifice of the intercostal vessels were some yellowish spots. The right external iliac and the right femoral were occluded by an organized thrombus. They felt like cords. The left femoral and popliteal arteries were also occluded. The basilar and the beginning of the posterior cerebral arteries were occluded by organized thrombi. The left radial artery about 1.5 cm. distal to the styloid process was occluded by a thrombus. There was an area of softening of the brain about the size of a pea near the corpus callosum and the upper part of the pons.

Comment.—This patient, aged 36, dated his symptoms back to the age of 20. During the progress of his illness, he had had many symp-

5. Czerna, Stephan: Arteritis Obliterans with Similar Changes in the Veins, Arch. f. inn. Med. **12**:213, 1926.

toms and physical signs pointing to vascular lesions in the heart and brain as well as in the extremities. The postmortem examination yielded observations consistent with the physical signs presented during life. The lesions characteristic of thrombo-angiitis obliterans were widespread throughout the vascular tree.

CASE 6 (Perla[6]).—A man, aged 44, had begun to complain, at the age of 27, of pain in the left foot; this was followed by gangrene of a toe, which was amputated. Later the other toes of the left foot were amputated, and one year later a midtibial amputation was performed on the left leg. At the same time, he began to have trouble with his right leg, and one year later it was amputated at the upper third of the lower part. Fourteen years after the onset of his trouble, gangrene developed in the ring finger of the right hand, which was amputated. Seven months prior to Perla's observation of the patient, the stump of the left leg began to be painful. It felt cold, was dark blue and soon became gangrenous; it was amputated above the knee. On admission to the hospital at this time, the patient complained of pain in both stumps. A gangrenous patch was observed in the right stump. He suffered from a great deal of pain. Both hands also had a purplish hue and became deeply cyanotic when lowered. When the arms were raised, however, both hands rapidly became pale. The results of the physical examination were otherwise negative. The urine was normal and the Wassermann reaction of the blood was negative. The blood pressure varied between 115 systolic and 90 diastolic and 135 systolic and 92 diastolic. A few months later his right leg was reamputated at the middle of the thigh, and one year later the index finger of his left hand was amputated. One year after this, the patient suddenly had a vomiting attack, became cyanotic and died. On postmortem examination, organized canalized thrombi were found involving the arteries of all the extremities, as well as the external iliac and the left coronary artery. The probable cause of death was thrombo-angiitis obliterans with extension of the process from the iliac arteries into the aorta as far as the renal arteries. The heart weighed 470 Gm. The main left coronary artery, beginning 1.5 cm. from its orifice in the aorta, showed an organized canalized thrombus almost completely occluding the lumen for a distance of 1.5 cm. The process here resembled that in the vessels of the extremities. The right coronary artery showed no abnormalities.

Comment.—The progress of the disease in this patient apparently could not be controlled. Almost all the vessels were involved. At an early age, the patient developed thrombo-angiitis obliterans, which made itself manifest in the lower extremities. Postmortem examination revealed the characteristic lesion of the disease also in the coronary artery.

CASE 7 (Buerger[7]).—A man, aged 35, a Russian, gave a history typical of thrombo-angiitis obliterans of the left lower extremity, for which amputation was

6. Perla, David: An Analysis of Forty-One Cases of Thrombo-Angiitis Obliterans, Surg. Gynec. Obst. **41**:21 (July) 1925 (case 3).

7. Buerger, Leo: Concerning Vasomotor and Trophic Disturbances of Upper Extremities, with Particular Reference to Thrombo-Angiitis Obliterans, Am. J. M. Sc. **149**:210, 1915 (case 9).

done in 1903, and a reamputation one month later. In 1905, an ulcer developed at the inner side of the right heel. Gangrene advanced rapidly and the right leg was amputated. Five years later, the disease involved the left upper extremity. Gangrene started in his fingers, giving rise to excruciating pain. On the amputation of his forearm, both the radial and the ulnar arteries were completely occluded and showed the typical lesions of thrombo-angiitis obliterans. Four years later, in April, 1914, the patient, in a condition of stupor, was again admitted to the wards of the Mount Sinai Hospital. His speech was incoherent and there were evidences either of some cerebral lesion, or of a vascular lesion in the brain. The condition of the right hand was of particular interest. Nowhere was there any evidence of ulcer or gangrene. The skin of the right hand was dry and atrophic. The fingers had a tapering appearance. The skin had lost its elasticity, the subcutaneous tissues had withered and neither the radial nor the ulnar arteries were palpable. The brachial artery, too, gave but the slightest impression of pulsation.

Comment.—This young man had had several amputations of the lower and upper extremities because of thrombo-angiitis obliterans; signs of a vascular lesion of the brain suddenly developed. In the presence of the known diagnosis, thrombo-angiitis obliterans, and the absence of arteriosclerosis, it may be assumed that the cerebral vascular lesion was due to the progressive activity of this disease.

CASE 8 (Lewis[8]).—A man, aged 47, of German extraction, admitted to the Johns Hopkins Hospital in December, 1926, had for the last seven years had pains in both calves. The pain had increased in severity and frequency, and practically prevented him from walking. Several years after the onset of pain in his legs, the same kind of pain developed in his right forearm, so that he was unable to work. Two years previous to admission, he was operated on for varicose veins, but the pains in his legs were not relieved. The intermittent limping persisted. On examination, the radial pulse could not be palpated on the right side; the left radial pulse was felt faintly, but the arteries were not sclerosed. Both feet were purplish. The dorsalis pedis and posterior tibial arteries could not be felt. The blood pressure could not be obtained on the right arm; on the left arm, it was 136 systolic and 90 diastolic. One night, the patient suddenly became hemiplegic and died.

On postmortem examination, the most interesting condition found was that in connection with the general arterial tree. At the level of the celiac axis, the aorta suddenly became reduced in diameter, so that it measured hardly more than 1 cm. There was an old organized thrombus that totally occluded the abdominal aorta, beginning at the level of the celiac axis and extending all the way to the bifurcation. From about 5 to 8 cm. below the celiac axis there was a small, crescent shaped channel which was the only channel that passed through this portion of the aorta. When a probe was passed through the channel from above downward, the channel was found to end about 5 cm. above the bifurcation, where it communicated directly with a comparatively large branch, which left the aorta and spread out into the surrounding tissue. Below this branch, there was no lumen within the aorta. It was totally blocked by an old organized thrombus, which presented, on section, a peculiar transparent appearance. A complete blockage of the celiac axis had resulted from a comparatively fresh thrombus, which

8. Lewis, Dean: Spontaneous Gangrene of the Extremities, Arch. Surg. **15**:613 (Oct.) 1927.

extended from the celiac axis into the lumen of the aorta or, perhaps, in the opposite direction. The portion of the thrombus that was in the lumen of the aorta communicated with the fresh thrombus lying between the exit of the celiac axis and the organized thrombus that filled the abdominal portion of the aorta. The beginnings of the common iliac arteries was occluded by old organized thrombi, which had many channels. The thrombosis affected the internal and external iliac arteries on both sides. The left external iliac artery, just before it became the femoral, was only partially occluded by a thrombus. This was also true of the right external iliac artery. In the femoral artery on the left side, extensive thrombotic changes were seen. None of the branches of the femoral group appeared normal.

In the right femoral region there was extensive thrombosis of the femoral artery and its branches. (All the main branches of the arch of the aorta showed sclerotic changes). A total occlusion of the second portion of the right subclavian artery was found; this extended into the axillary and brachial arteries. The right external carotid was closed by a thrombus; its point of origin from the common carotid was represented by a puckered scar. About 2.5 cm. above the bifurcation of the common carotid, the internal carotid artery was plugged by an organized thrombus, through which passed small, newly developed channels. In the skull, a similar thrombotic process filled the internal carotid at the point of anastomosis with the vessels from the opposite side.

Comment.—The most interesting observation was that, with the lesion so widespread, there was so little evidence of circulatory impairment. Postmortem examination showed to what great extent this disease can be distributed throughout the vascular system.

Case 9 (Thomas[9]).—A Jewish physician, aged 44, in August, 1918, had a sudden attack of excruciating pain with a sense of constriction in the lower part of the chest. The patient was extremely cyanotic. His pain was so severe that it could be relieved only with ¼ grain (0.048 Gm.) of morphine. He remained in bed for ten days with a slight fever. The pulse rate varied from 100 to 120. His physician diagnosed the condition as "angina pectoris." The severity of his pain, however, the cyanosis, the elevation of temperature and the rapid pulse rate made the diagnosis of coronary thrombosis more probable. Three years later, he began to have severe pains in his hips and legs, so that he could not walk even short distances without stopping to rest.

The physical examination revealed conditions essentially normal, except that no pulsations could be felt in the dorsalis pedis, the posterior tibial and the femoral arteries on either side. A diagnosis of thrombo-angiitis obliterans was made.

Comment.—This patient presented a rather unusual clinical picture in that there was an absence of pulsations in the main arterial channels throughout both lower extremities, yet there was no evidence of gangrene. Shortly prior to the attacks of intermittent claudication, he had this severe pain in the chest, which was probably an attack of coronary thrombosis. The story is interesting in that he probably had the same

9. Thomas, H. M., Jr.: Persistent Leucocytosis in the Early Stages of Thrombo-Angiitis Obliterans, Am. J. M. Sc. **165**:86 (June) 1923.

pathologic process and the same sequence of symptoms in the coronary arteries as in the arteries of the extremities, that is, first spasm and later complete occlusion.

Case 10 (Telford and Stopford).[10]—A man, aged 40, born in England, at the age of 30 had noticed pain in the right calf on walking. Shortly after, a similar pain occurred in the left calf. The pain so increased in severity that for a period of two years he was able to walk only short distances with the aid of crutches. He then noticed that his right leg was slightly swollen and that the toes were purplish. During this time, he had a sore on the front of the ankle, which took eighteen months to heal. Two years before the period in question, however, the left leg began to get worse. The foot was "always stone cold," and a small septic focus appeared on the inner side of the great toe.

Except for a digestive trouble suggestive of duodenal ulcer, his previous condition was good. In his earlier days he had been a most enthusiastic fisherman and had spent much time wading, a habit to which he attributed his troubles.

Examination.—The right leg was much wasted from disuse, the muscle power was good and sensation was everywhere normal. The femoral pulse was normal, but the popliteal pulse was barely to be felt, and there was no pulse below this level. The left foot was dull red; there was edema about the dorsum of the foot and a small onychia of the great toe. There was no pulsation in the femoral artery or at any point below this. One night in January, 1924, this patient was seized with severe abdominal pain, and was found to be suffering from a perforative lesion, presumably of the duodenum, as he had for some time shown symptoms suggestive of duodenal ulcer. Laparotomy was done, and a large perforation of the anterior wall of the first stage of the duodenum was sutured; the operation was completed by posterior gastro-enterostomy. As far as his condition allowed, an exploration was made to ascertain the condition of the intra-abdominal vessels. No pulsation could be felt in the common, internal and external iliac arteries of the left side; these vessels were plainly felt as immobile cords.

He made an excellent recovery from the operation, but in April, 1924, ten and a half years after the onset of the disease, the whole of the left foot rapidly became gangrenous, the condition having spread from the old onychia of the great toe. A supracondylar amputation was done through the left thigh on the following day; the femoral artery at the level of the section was open and normal. The wound healed without incident. The histologic observations were characteristic of thrombo-angiitis obliterans.

Comment.—There was an opportunity to explore the abdominal vessels during life. The exploration revealed an absence of pulsation in the common internal and external iliac arteries of the left side, and these vessels were plainly felt as immobile cords. This man had a duodenal ulcer which perforated. Whether there was any relation between the duodenal ulcer and thrombo-angiitis obliterans is difficult to say, but it is of some significance that in case 1 of our series the patient also had a duodenal ulcer.

Another interesting observation is that, although the common internal and external iliac arteries of the left side were totally occluded, the

10. Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. **2**:1035, (Dec. 6) 1924.

femoral artery at the point of amputation was open. This point bears out some observations that we made in our own material—that an organized thrombus may be found in one part of an artery causing occlusion while the vessel slightly above or below this thrombus is perfectly free from obstruction; some distance either above or below this thrombus, another occlusion may be found.

In an interesting and important study, Meleny and Miller [11] injected an opaque solution into the vessels of extremities which had been amputated for thrombo-angiitis obliterans and clearly demonstrated the patchy appearance of the vessels. They showed that the opaque mass may fill part of a vessel, leave the artery by a collateral branch and then, by a circuitous route, appear again in the same vessel below.

FURTHER CASES FROM THE LITERATURE

In addition to the cases cited at length, we may also refer to Brown and Henderson's [3] two cases of thrombo-angiitis obliterans in young men, both of whom showed evidence of coronary thrombosis.

Lemann [12] had under observation two patients with thrombo-angiitis obliterans both of whom had coronary occlusion.

Buerger, in his book on "Circulatory Disturbances of the Extremities," reported the autopsies in four cases of this disease occurring in young men. He stressed strongly the precocious arteriosclerotic changes in the blood vessels of these patients, particularly in the coronary arteries. One of the patients showed definite occlusion of the mesenteric vessels resulting in gangrene of the intestines. We have purposely not included these cases on account of the fact that there was such gross evidence of occlusion due to arteriosclerosis. However, it seems that in such young persons with a known diagnosis of thrombo-angiitis obliterans of the extremities there might be some relationship between the early atheromatous changes in the visceral vessels and the characteristic lesions of thrombo-angiitis obliterans of the vessels of the extremities.

Oppel,[13] of Leningrad, called attention to the fact that patients with suprarenal arteriosis [14] sometimes die of intestinal gangrene caused by thrombosis of the mesenteric arteries. He also reported the case of a patient who had thrombosis of the cervical arteries, which caused a hemiplegia. Some patients, he said, die of angina pectoris, and a post-

11. Meleney, F. L., and Miller, C. G.: A Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. **81**:976, 1925.

12. Lemann, I. V.: Personal communication to the authors. The case reports are to appear in the American Journal of Medical Sciences.

13. Oppel, V. A.: Spontaneous Gangrene of the Extremities and Suprarenalectomy, Lyon chir. **14**:1 (Jan.-Feb.) 1927.

14. Oppel uses the term "suprarenal arteriosis" synonymously with spontaneous gangrene and thrombo-angiitis obliterans.

mortem dissection shows that the angina was caused by thrombosis of the coronary arteries. Therefore Oppel concluded that this disease is not local but generalized, and that every artery of the human body may be affected by thrombosis.

Constam [15] also reported four cases of this disease occurring in the upper extremities in young men with no evident involvement of the lower extremities. Koyano [16] in 125 cases found an associated involvement of the upper and the lower extremities in 30 per cent. According to Allen and Brown,[17] of forty patients with definite involvement of the lower extremities twenty-four, or 60 per cent, showed on careful examination either complete or partial closure of the ulnar or radial arteries.

A patient under our observation at the time of writing, who had thrombo-angiitis obliterans, gave a history of intermittent claudication of twenty years' duration and at the time showed nothing more than an ulcer over the terminal phalanx of the left great toe, yet no pulsation in the main arterial channels could be felt throughout the entire left lower extremity. An opportunity was afforded to explore the left external iliac artery for some distance when the left femoral vein was ligated. There was absence of pulsation in the left external iliac artery as far as could be felt. In the right radial artery, the pulsation was much weaker than in the left, and the blood pressure in the left arm was 136 systolic and that in the right 110 systolic. This marked variation in blood pressure and pulsation of both radial arteries, together with the absence of pulsation from the highest point at which the external iliac artery could be felt throughout the entire lower extremity, makes it hard to believe that the disease is limited to the extremities and stops abruptly at the particular point in the external iliac artery that could be felt.

Comment.—From the review of these cases there can remain no doubt that thrombo-angiitis obliterans is a general disease that may attack any part of the vascular system. That it frequently involves the blood vessels of the brain, neck, thorax and abdomen, as well as of the extremities, is proved.

The reason that the characteristic signs and symptoms of thrombo-angiitis obliterans do not appear frequently in the upper extremities and only rarely in other parts of the body may be looked for by analogy

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15. Constam, G. R.: Primary Involvement of the Upper Extremities in Thrombo-Angiitis Obliterans, Am. J. M. Sc. **174**:530 (Oct.) 1927.

16. Koyano, K.: A Clinical Study of 120 Cases of Thrombo-Angiitis Obliterans Among the Japanese, Acta scholae med. univ. imp. Kioto **4**:489, 1921-1922.

17. Allen, E. V., and Brown, G. E.: Thrombo-Angiitis Obliterans: Clinical Study of 200 Cases: Etiology, Pathology, Symptoms, Diagnosis, Ann. Int. Med. **1**:535 (Feb.) 1928.

in what takes place in extensive arteriosclerosis in the vascular tree; on postmortem examination in the latter case, one finds marked involvement of the vessels in the upper extremities and in the abdomen, but seldom observes arteriosclerotic gangrene in the upper extremities or lesions in the abdominal viscera. The greater demand made on the circulatory channels of the lower extremities because of static conditions may favor the more rapid development of the lesion. Moreover, the feet are more susceptible to slight injuries from deformities of the nails and from calluses, which are frequently the starting points of gangrene.

We know, moreover, that it is possible to maintain a sufficient circulation to keep up the nutritional balance of a part in the presence of occlusion of the main arterial trunk through collateral or anastomosing branches. If this is true for arteriosclerosis, it is more so for thrombo-angiitis obliterans. For we know from the work of Meleney and Miller,[11] of Lewis,[8] and of Lewis and Reichert [18] that collateral circulation and free anastomosis develop in inverse proportion to the extent and rapidity of the vascular occlusion. For that reason, because the process of occlusion is slower and more gradual in thrombo-angiitis obliterans, there is a tendency in this disease to produce a more liberal collateral circulation.

It might be of interest at this point to compare the symptom complex that occurs as a result of arteriosclerosis of the lower extremities with that from the same condition in the coronary vessels. The earliest symptoms in the lower extremities are usually intermittent claudication on walking a variable distance; the patient complains of severe cramp-like pains in the calves; he must stop and rest before he can continue. Later, there is occlusion of the peripheral vessels and possibly gangrene. A parallel syndrome occurs in sclerosis of the coronary arteries; the earliest symptom is a feeling of constriction through the chest or severe pain over the cardiac area. On exertion, the patient must stop, if walking, and rest before continuing. The later manifestation of coronary sclerosis is a distinct narrowing of the lumen of these vessels or complete occlusion. In thrombo-angiitis obliterans, the symptom complex is, likewise, first partial occlusion and spasm of the vessel causing intermittent claudication, and later complete occlusion. The analysis of the cases cited and the postmortem observations in some of them indicate definitely that a pathologic process similar to that which takes place in the extremities also occurs in the coronary arteries and vessels of the brain.

What we have previously stated in regard to the unusual development of the collateral circulation in the presence of thrombo-angiitis

18. Lewis, D., and Reichert, F. L.: The Collateral Circulation in Thrombo-Angiitis Obliterans, J. A. M. A. **87**:302 (July 31) 1926.

obliterans is also true of the blood supply to the myocardium, particularly so in the light of the important work of Gross,[19] who demonstrated that a liberal anastomosis existed between the branches of the coronaries and that the coronary vessels were not terminal end arteries. This work was substantiated later by Spalteholz.[20] Oberhelman and LeCount [21] drew similar conclusions from their studies. The recent work of Wearn [22] further demonstrated that there is yet another channel by which the heart muscle may receive a sufficient supply of blood in the face of coronary obstruction; that is, by way of the thebesian vessels.

The question arises: Why do we not see more patients with coronary disease due to thrombo-angiitis obliterans and why has the observation not been made more frequently?

In view of the definitely established fact that the lesions of thrombo-angiitis obliterans do occur in the coronaries, as was shown by the postmortem observations in some of the cases cited, the suggestion is near at hand that the occasional cases of angina pectoris and coronary thrombosis that occur early in life without any evidence of vascular disease elsewhere, may, in some instances, at least, be due to thrombo-angiitis obliterans of the coronaries and not to arteriosclerosis.

The reason that it is not found more frequently on postmortem examination may be that the disease is characterized by a chronic course and that, as years go on, arteriosclerotic changes also take place in the vessels affected by thrombo-angiitis obliterans. The latter may be entirely overlooked in the presence of arteriosclerosis.

PATHOLOGY

From our studies of the gross pathologic changes of this disease, we have noted not infrequently that an organized thrombus may be found in one part of an artery causing occlusion and the vessel slightly above or below this thrombus be found perfectly free from any obstruction; some distance either above or below this thrombus another occlusion may be found. This would tend to show that the disease does not start from one special focus in a vessel, but rather arises at various levels, at different periods. This observation is based on the microscopic observations which, for example, as in one of our cases, show a well organized thrombus in the posterior tibial artery and a subacute lesion in the lower end of this vessel. These observations tend to indicate that this disease is disseminated by the blood stream.

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19. Gross, L.: The Blood Supply to the Heart, Its Anatomical and Clinical Aspects, ed. 1, New York, Paul B. Hoeber, 1921.

20. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924.

21. Oberhelman, H. A., and LeCount, E. R.: Variations in Anastomosis of Coronary Arteries and Their Sequences, J. A. M. A. **82**:1321 (April 26) 1924.

22. Wearn, J. T.: The Rôle of the Thebesian Vessels in the Circulation of the Heart, J. Exper. Med. **47**:293 (Feb. 1) 1928.

It is probable that the disease attacks the larger vessels first, then, in the late stages, obliterates the arterioles and capillaries. This is shown by the fact that gangrene does not occur, as a general rule, until late in the disease. We know from the studies of Meleney and Miller [11] and the observations of Lewis [8] that there is a vigorous attempt at the formation of a collateral circulation to compensate for the occlusion of the larger vessels. It would be necessary, therefore, for the smaller arterioles and capillaries to hypertrophy and dilate to take care of this circulation; it is not unusual for this disease to exist for many years with no evidence of impairment of the circulation, although pulsation in the dorsalis pedis and posterior tibial arteries is absent. This points out that the circulation is taken on by the small arterioles, and that for some unknown reason the larger vessels suffer most, although some of the smaller vessels no doubt are also attacked late in the disease.

The collateral circulation in this disease evidently plays the most important rôle, and the ability of the arteries to make and produce new and larger collaterals often is the deciding factor as to whether or not the patient will lose a member. The mechanism of the formation of collateral circulation is not altogether obvious or easily explained. It is a remarkable phenomenon that the main arterial channels become totally occluded without the part becoming gangrenous. Clinically, it is well recognized that with occlusion of the main vessels the collateral circulation has taken the place of the main arteries. Bolognesi [23] performed experiments to determine the effect of ligating the external iliac artery in dogs. He found that the gluteal branches of the iliac artery, and especially those of the inferior or ischiatic gluteal artery, took part in the formation of the collateral circulation, becoming larger and richer in branches. These branches anastomosed fully with the femoral branches. Bernheim and Sachs,[24] in studies on the collateral circulation of the lower extremities of patients examined post mortem, found that the circulation to the extremities, even though the femoral artery was occluded above the origin of the profunda femoris, could be taken care of by way of the gluteal arteries in the presence of profound arterial disease. They observed in cases in which this condition existed that the gluteal vessels grew much larger and that they offered a direct line of blood flow to the tissues of the lower part of the leg and foot through the branches that run along with the sciatic nerve. In normal limbs these branches were almost invisible. That this can be accomplished is evidenced in a case reported by Dumas and Ravault,[25] in which the

25. Dumas, A., and Ravault, P.: Physiologic and Histologic Investigations on the Circulatory Conditions in the Left Leg, the Femoral Artery of Which Had Been Ligated in 1870, Lyon chir. **24**:387 (July-Aug.) 1927.

23. Bolognesi, quoted by Buerger (footnote 27).

24. Bernheim, B. M., and Sachs, L.: Notes on the Collateral Circulation in Blood Vessel Diseases of the Lower Extremities, Ann. Surg. **86**:417 (Sept.) 1927.

femoral artery had been ligated in the upper part of Scarpa's triangle fifty-six years before. The patient was a man who had been wounded in the left leg by a bursting shell in the Franco-Prussian war of 1870. He was examined prior to his death, which occurred on Nov. 21, 1926. There was no evidence of vascular disturbance at that time. At autopsy, it was found that an adequate collateral circulation had been established, so that the femoral artery shortly below the ligature was of normal caliber and the popliteal, anterior and posterior tibial arteries were the same on one side as on the other.

The veins in thrombo-angiitis obliterans present a condition similar to that of the arteries. Some authors [3] stated that about 30 per cent of their patients showed a superficial phlebitis; occasionally one sees a deep phlebitis that is characterized by more or less edema, which some investigators [26] use as a sort of indicator as to whether an amputation should be done above or below the knee. A superficial phlebitis developed in one of our patients while he was in the hospital (case 2). This was probably the condition that Buerger [27] referred to as migrating phlebitis.

Pathologic Histology.—The pathologic changes are characteristic and certainly indicate that the initial process is inflammatory. One first notices in a vein a fresh clot made up of polymorphonuclear leukocytes, lymphocytes, mononuclear leukocytes, wandering cells and red corpuscles. As the lesion progresses, foreign body giant cells are seen. This phase is present in veins in which superficial phlebitis has occurred. Attention was directed to these foreign body giant cells first by Buerger.[28] The inflammatory cells soon invade the intima, media and adventitia, so that in the process of healing the vein, artery and nerve are closely bound together by the newly formed inflammatory tissue. This tissue soon becomes well organized, and it is with difficulty that the vein, artery and nerve are separated. This process appears to be a phase of a defense reaction that occurs in inflammation and is really a reparative process.

Since it has been proved [17] that there are no changes in the blood to cause the formation of a clot or thrombus, it is fair to assume that the clot is due to trauma to the inner wall of the vessel. As this characteristic clot, made up of fibrin, polymorphonuclear leukocytes, wandering cells, mononuclear leukocytes and giant cells, begins to organize, strands of fibrous tissue arise from the periphery made up of young connective tissue cells, mostly fibroblasts. This process goes on until there is

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26. Allen, E. V., and Meyerding, H. W.: Surgical Procedure in Obliterative Vascular Disease (Thrombo-Angiitis Obliterans): A Report of 45 Cases, Surg. Gynec. Obst. **44**:260, 1928.

27. Buerger, Leo: Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924, p. 214.

28. Buerger (footnote 27, p. 320).

complete organization of the clot. In the process of the connective tissue change there are formed new small blood vessels lined by a single layer of endothelium and somewhat similar to the capillaries in healed or healing scar tissue. The pathologic picture is entirely that of an inflammatory process with the characteristic picture of healing. This process keeps repeating itself in various vessels at various levels and at different times, so that the condition is characterized by chronicity, and it is this chronic inflammatory process that slowly occludes the vessels. It has aptly been described, therefore, as a race between the formation of a collateral circulation and the occlusion in the main arterial channels. That this process is characterized by chronicity is proved by the fact that some patients with this disease have dated their symptoms back twenty years. We had one patient in our series who was positive that he had had symptoms of intermittent claudication for fully twenty years before the onset of the trophic disturbance.

SUMMARY

This study covered thirty-four cases of thrombo-angiitis obliterans; twenty-seven cases came under our own observation and seven were collected from the literature. All the cases occurred in persons under 50 years of age, who had had the disease for many years previous to the manifestations of definite nutritional disturbance. None of the patients, therefore, were of the "arteriosclerotic age" when the disease started. In the postmortem examinations which we collected, in which evidence of arteriosclerosis was found, the arteriosclerotic process was obviously not responsible for the condition, but had been superimposed on the long standing thrombo-angiitis obliterans.

An analysis of our material shows that the disease is of a slow, insidious onset, and of many years' duration. The vessels involved are slowly occluded and, owing to this slow occlusion, there is an opportunity for collateral circulation to be established. This explains the fact that the nutrition of the part supplied by the occluded vessel is maintained, and a patient may go on for many years without nutritional disturbance of the parts involved. We have also seen that the process in the arterial tree does not spread by extension from a single focus, but may occur at different levels in an artery and in various vessels at different periods.

Above all, the analysis of our cases, and of those collected from the literature in which necropsies were performed, demonstrates that this disease is not confined to vessels of the extremities, as is generally accepted, but is a generalized disease that may affect any part of the arterial tree, including the coronary arteries, the abdominal arteries and the arteries of the brain.

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THIRTY-NINTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY *

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CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—MacAusland [1] reviewed the history of the operative treatment of congenital dislocation of the hip. According to him, the patients who should receive operative treatment are: (1) children from 4 to 8 years of age, in whom one or two closed manipulations have failed; (2) children over 8 years of age, and (3) adults with marked deformity or arthritic symptoms. The choice of operation depends on the existing deformity and to some extent on the age of the patient. Simple replacement of the head into the acetabulum, or some form of reconstruction operation with or without the formation of a shelf, or arthrodesis are the procedures one has at one's disposal. The author describes in detail his operative technic and the postoperative care of the patient.

NUTRITIONAL DISTURBANCES

Activated Ergosterol.—An editorial in *The Journal of the American Medical Association* [2] says that recent studies of Rosenheim and Web-

* Submitted for publication, Sept. 12, 1929.

* This Report of Progress is based on a review of 238 articles selected from 390 titles dealing with orthopedic surgery appearing in medical literature between Feb. 15, 1929, and June 1, 1929. Only those papers which seem to represent progress have been selected for note and comment.

1. MacAusland, W. R.: Surg. Gynec. Obst. **47**:697 (Nov.) 1928.

2. Editorial: The Precursor of Vitamin D: Ergosterol, J. A. M. A. **91**: 1110 (Oct. 13) 1928.

ster in London make the position of ergosterol as a parent substance of vitamin D appear unique. They have presented evidence which strengthens the assumption that only a molecular structure such as that possessed by ergosterol enables an esterol to be photochemically converted into vitamin D, and confirms the evidence already available for the view that ergosterol is the specific parent substance of vitamin D. Fortunately, the substance is obtainable with comparative ease from natural sources, so that there need be no limitations to its availability for therapeutic use if this is finally established on a sound basis.

Karelitz [3] discussed the value of ergosterol, a substance formerly isolated from mushrooms, ergot and yeast, when activated by a magnesium spark of a mercury vapor quartz lamp. He cited evidence to prove that it is 20,000 times as effective as cod liver oil in combating rickets.

Hess, Bills and Honeywell,[4] studying the variability of the antirachitic potency of cod liver oil, found that contrary to current opinion, this varies inversely with the amount of oil in the livers. From extremely "poor" livers, oil was extracted which was 200 times more potent than high grade cod liver oil and far more potent than any oil heretofore assayed. The oil from livers of individual cod may vary 1,000 times in their antirachitic value.

Renal Rickets.—Kellet [5] reported a case of renal rickets in which the inorganic phosphorus in the blood was below normal (3.82 mg. per hundred cubic centimeters). The blood urea was 158 mg. and the calcium 10.4 mg. It has been suggested that the bone changes in renal rickets are due to an increased retention of phosphorus because of the failure of the kidney to excrete phosphorus. This case appears to refute this view. Kellet reported benefit in this case from ultraviolet therapy, whereas in most cases of renal rickets the patients are made worse by actinotherapy.

DISTURBANCES OF GROWTH

Displacement of the Upper Femoral Epiphysis.—In a review of twenty-seven cases of displaced upper femoral epiphysis, Badgley [6] expressed the belief that at adolescence there is a change in the anatomic relationship of the head to the neck of the femur, and that there may be a thinning of the periosteum at the time of puberty, as pointed out by Key. These factors plus obesity and rapid growth, which are char-

3. Karelitz, S.: Activated Ergosterol in Treatment of Rickets, Am. J. Dis. Child. **36**:1108 (Dec.) 1928.

4. Hess, A. F.; Bills, C. E., and Honeywell, Edna M.: Antirachitic Potency in Relation to Volume of Oil in Liver of Cod, J. A. M. A. **92**:226 (Jan. 19) 1929.

5. Kellet, C. E.: Proc. Roy. Soc. Med. **22**:142 (Dec.) 1928.

6. Badgley, C. E.: Displacement of Upper Femoral Epiphysis, J. A. M. A. **92**:355 (Feb. 2) 1929.

acteristic of these patients, are important. The endocrine dysfunction is, he thinks, of little significance. The necessity of early treatment is emphasized. In the preslip stage he advised a plaster spica with the hip in abduction and internal rotation for six weeks and then the use of a walking caliper. The cases in which displacement has occurred recently require the Whitman manipulation, a plaster spica for five weeks, at the end of which time physiotherapy is started. At the end of eight weeks, a splint is given and the patient allowed to walk. In cases in which the epiphysis has been displaced as long as four months, Badgley would employ the curved osteotomy of Wilson. In young adults in whom healing has occurred the Whitman reconstruction operation is required, while in older patients fusion seems the best method of treatment.

[ED. NOTE.—Obestiy is not always a characteristic of this condition, and we are not prepared to say that endocrine dysfunction is of little significance. As yet we know too little of this condition to make such statements.]

Achondroplasia.—Warner [7] described and gave illustrations of twins, aged 10½ years, one of whom was an achondroplastic dwarf and the other a normal child. He argued from this that achondroplasia is an inherited variation and is not due to any maternal infection or influence.

VASCULAR DISEASES

Thrombo-Angiitis Obliterans.—Allen and Smithwick [8] reported their results in twenty-five patients with peripheral vascular disease, treated by foreign protein shock. Two of the cases were undoubtedly of vasomotor origin; thirteen were of presenile gangrene, clinically thromboangiitis obliterans; six were of arteriosclerotic gangrene, including those with associated diabetes; and four were unclassified. Nineteen patients were admitted with ulceration, only six had pulsating vessels, and nineteen were completely disabled. The number of treatments varied from one to fifteen over periods varying from three weeks to fifteen months, without deleterious effect on the patient. Of the nineteen patients entering with complete disability, five had major amputations and are included in the group of seven patients considered as unrelieved. Twelve of the nineteen patients with complete disability have been able to return to their former work. Nonspecific foreign protein (typhoid vaccine given intravenously) gives a definite reaction much like that observed following periarterial sympathectomy with a definite relief from pain and a beneficial change in the appearance of the lesions. The reaction can be repeated at intervals of seven days

7. Warner, Allan: Brit. M. J. **2**:983 (Dec. 1) 1928.

8. Allen, Arthur W., and Smithwick, R. H.: Use of Foreign Protein in Treatment of Peripheral Vascular Diseases, J. A. M. A. **91**:1161 (Oct. 20) 1928.

or more with subsequent healing of the ulcerations. The treatment should be combined with proper hygiene and minor surgical operations when necessary, as it enhances the safety of such procedures.

The end-results in ninety periarterial sympathectomies were reported by Muller.[9] In arteriosclerotic patients twelve operations were performed, two of these being relieved from pain. In no cases of arteriosclerosis was gangrene checked by sympathectomy. Seventeen operations were performed for thrombo-angiitis obliterans. Two of these were followed by definite improvement. Pain was relieved, but no increase in the circulation was found. The operation was performed in three cases of Raynaud's disease with relief from symptoms in two of the cases. The author expressed the belief that the operation is of particular value in chronic ulcers of the extremities which have not yielded to the usual therapeutic measures.

Archibald [10] found that pain from arterial disease of organic origin was not relieved by periarterial sympathectomy in more than half his cases. Ramisection was necessary in some to relieve pain.

Philips [11] reported a number of cases of neurocirculatory disease in which roentgen treatment was given. He stated that irradiation given over the spinal segments controlling the affected parts overcomes an overirritated status of the sympathetic ganglions. Relief from pain may occur immediately or several weeks later, followed by improvement in the circulation.

[ED. NOTE.—These reports are significant in that they show the widespread interest in conservative measures as against amputations in vascular diseases of the extremities. The last report is of an untried field, as far as we are aware, and should be repeated by other roentgen therapists.]

NEUROLOGIC CONDITIONS

Traumatic Ulnar Neuritis.—Platt [12] divided ulnar neuritis into the following clinical groups:

1. Primary neuritis resulting from contusions of the nerve or from supracondylar fracture or dislocations of the elbow.

2. Secondary neuritis complicating fractures of the lower end of the humerus or dislocations of the elbow.

3. Delayed neuritis, a sequel to external condyle fractures or caused by recurrent dislocation of the nerve.

In the milder forms of neuritis, resting the nerve in a relaxed position usually suffices; but in the severe form, the operative treatment

9. Muller, G. P.: Ann. Surg. **88**:474 (Sept.) 1928.
10. Archibald, E.: Ann. Surg. **88**:499 (Sept.) 1928.
11. Philips, H. B.: M. J. & Rec. **128**:559 (Dec. 5) 1928.
12. Platt, Harry: Surg. Gynec. Obst. **47**:822 (Dec.) 1928.

is usually indicated. The technic of anterior transposition of the nerve is described in detail. Special emphasis is placed on preservation of the small branches of the nerve and its blood supply, and on careful fixation and protection of the nerve in its transplanted position.

Surgery of the Sympathetic System.—Leriche [13] concluded from his observations that the sympathetic nervous system acts like a vast sensory cistern with reflex associations everywhere. Every section of a sympathetic chain is followed by active vasodilatation that is more or less lasting. Paresis of vessels never occurs. Section, also, is always followed by cicatricial neuroma. The author reports the results in 400 cases of ganglionectomy, ramisection and arterial sympathectomy. Gratifying results are reported in the neuralgias following severe injuries or amputations of limbs and in chronic ulcers.

Von Lackum [14] found no reason to withdraw his statement of 1926 that "there is no longer any doubt as to the efficacy of sympathetic ramisection in certain cases of spastic paralysis." Fifty-four lumbar and ten cervical ramisections have been performed. Good results can be obtained only in patients with the best mentality. Von Lackum felt that this procedure offers an effective means of relief in many cases of spastic paralysis in children.

TUBERCULOSIS

Roentgen Diagnosis.—Ghormley and Bradley,[15] who believe that the study of a single roentgenogram of a tuberculous spine is of interest from a diagnostic standpoint, but from a prognostic standpoint is of much less value than a series of roentgenograms on the same patient, gave the result of their study of seventy such pictures taken at the New England Peabody Home for Crippled Children. These pictures were taken at four month intervals over a period of from two to five years or more. The patients have for the most part been treated by conservative methods—recumbency during the early stages of the disease, combined with heliotherapy, fresh air and the usual modern requisites in good general care of tuberculous patients. These estimates would therefore probably vary somewhat in a series of cases in which operation had been performed.

From this study the writers concluded that:

1. Calcification in a lesion does not necessarily mean satisfactory healing.

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13. Leriche, R.: Ann. Surg. **88**:449 (Sept.) 1928.

14. Von Lackum, H. LeRoy: Sympathetic Ramisection in Spastic Paralysis, J. A. M. A. **92**:139 (Jan. 12) 1929.

15. Ghormley, Ralph K., and Bradley, John I.: J. Bone & Joint Surg. **10**:796 (Oct.) 1928.

2. Clearing or reestablishment of bony detail is a much better indication of healing.

3. Bony fusion or bony block is a favorable sign.

4. Decrease in the size of the abscess is a favorable sign, while increase in the size of the abscess is decidedly an unfavorable sign.

5. Paravertebral abscesses accompanying dorsal Pott's disease are dangerous in that they cause a much wider destruction than the original lesion. A mechanical pulsating force must play a part in their production.

6. It is suggested that early eradication of such abscesses might be attempted, but the danger of establishing a permanent sinus is serious.

Treatment.—Clavelin and Sicard [16] advocated the use of intravenous administration of calcium chloride followed immediately by ultraviolet irradiation. This was suggested to them by the work of Weill and Guillamin on calcium fixation. They have worked out a definite dosage and plan of treatment, and feel that they have had favorable results in twenty-eight cases.

POLIOMYELITIS

Use of Convalescent Serum.—According to Aycock, Luther and Kramer,[17] the rationale of giving convalescent serum in poliomyelitis is based on three facts:

1. One attack of poliomyelitis apparently confers immunity from the disease.

2. The blood serum of human beings and of monkeys who have had the disease neutralizes the virus.

3. Convalescent serum when tested experimentally exerts a protective action against the virus.

The blood, after fever and muscle tenderness have subsided, is collected into a special bottle (from 400 to 500 cc. from adults and from 200 to 300 cc. from children). It is then incubated for one hour at 37 C., and the serum is drawn off into an aspirating bottle. The serum is given both intraspinally and intravenously. Twenty cubic centimeters of the spinal fluid is withdrawn, and the same amount of serum is introduced into the spinal canal; following this, 60 cc. of the serum is given intravenously. The intraspinal dose is repeated the following day, and if the fever persists, the intravenous dose may again be given. Reactions are frequent but usually not severe.

Tendon Transplantations.—Naughton Dunn,[18] in his presidential address to the orthopedic section of the Royal Society of Medicine,

16. Clavelin and Sicard, André: Presse méd. **36**:227 (Feb. 22) 1928.

17. Aycock, W. L.; Luther, Elliott H., and Kramer, S. D.: Technic of Convalescent Serum Therapy in Poliomyelitis, J. A. M. A. **92**:385 (Feb. 2) 1929.

18. Dunn, Naughton: Proc. Roy. Soc. Med. **22**:243 (Dec.) 1928.

London, on the surgery of the muscles and tendons in relation to infantile paralysis, emphasized the fact that division of tendons and muscles is seldom necessary for the correction of deformity. In Dunn's opinion, no tendon should be divided or lengthened unless the surgeon is satisfied, as a result of his experience, that (1) correction of the deformity will improve function; (2) elongation or division of tendons is necessary to correct that deformity, and (3) the power of the shortened muscle or tendon cannot be utilized by tendon transplantation at the time of the operation. Dunn quoted flexion deformity of the hip to illustrate this axiom. The operative correction for flexion deformity of the hip joint that is commonly advised weakens the tensor fascia femoris and the gluteus medius; and yet no splintage can mask the limp resulting from paralysis of the gluteus medius, and Legg's operation of transplanting the tensor fascia femoris is the usual operation recommended to replace its function. Dunn therefore strongly urged the gradual correction of flexion contracture of the hip, thereby preserving muscles that might be badly needed for transplantation. Dunn stated that the successful transference of muscle power to a new insertion, given a good surgical technic, is mainly dependent on the recognition of the group action of muscles. In the foot, for example, there are for practical purposes only two groups of muscles: (1) the anterior tibial, in action in dorsiflexion of the foot; (2) the peroneal and posterior tibial muscles, associated in action with the tendo achillis in plantar flexion. Any of the anterior tibial muscles can successfully replace one another, but no tendon from the peroneal or posterior tibial group will effectively replace the loss of active dorsiflexion. In the upper limb where the action of individual muscles is more specialized, reeducation of an individual tendon to act apart from its group is more practicable. In the technic of transplantation, Dunn expressed the belief that the important facor is the degree of tension under which the tendon is sutured. The method of attachment—whether to bone periosteum or tendon—and the preservation of the tendon sheath, he considers of minor importance. For weakness of the tibialis anticus, Dunn performs the operation he calls "tendon fusion." All the anterior tibial tendons above the ankle are sutured together, the tension on individual tendons varying according to the previous tendency to inversion or eversion of the foot. While recognizing tendon transplantation as helpful, Dunn expressed the belief that it does not by itself produce spectacular success and that joint fusions are frequently needed in addition.

[ED. NOTE.—Naughton Dunn's observations on lengthening muscles in infantile paralysis are well taken.]

PYOGENIC INFECTIONS

Osteomyelitis.—Phemister,[19] writing on the unusual forms of osteomyelitis, listed sclerosing osteomyelitis, localized diaphyseal osteomyelitis, nonsuppurative or fibrous osteomyelitis, chronic hemorrhagic osteomyelitis and osteitis fibrosa cystica. In sclerosing osteomyelitis, there is a wide diffusion of the infection without necrosis. Pain of varying intensity is the only symptom, and the patient is usually relieved by opening the sclerosed bone. Localized osteomyelitis in the shaft may be acute or chronic; pus is found only very early, and later the necrotic tissue is replaced by fibrous tissue. Areas of nonsuppurative osteomyelitis develop rather silently and are often mistaken for neoplasms. In chronic hemorrhagic osteomyelitis, the diseased tissue is stained brown from the blood pigments. It runs a chronic mild course, and the walls of the diseased area show the signs of an inflammatory process. Osteitis fibrosa cystica may be single or multiple and usually appears during the growing period. The walls of such cysts are definitely inflammatory. It is often difficult to differentiate such tissue from benign giant cell tumor.

ARTHRITIS

The Synovial Fluid in Arthritis.—Forkner, Shands and Poston[20] studied the bacteriology and cytology of the synovial fluid in sixty-three cases of chronic arthritis. Of these fifty-two were infectious, nine hypertrophic and two both infectious and hypertrophic arthritis. Organisms were recovered in fourteen cases, eleven of these being *Streptococcus viridans,* two the gonococcus and one *Staphylococcus aureus.* Bacteriologic examination of the regional lymph nodes gave positive cultures in 48 per cent. The cells in the synovial fluids of thirty-three patients were studied by the supravital technic. The polymorphonuclear neutrophils were increased in all cases, when organisms were recovered from the fluid. In synovial fluids in which no organisms were obtained, the monocytes and lymphocytes gave higher counts.

Deformity of Knee in Arthritis.—Swaim[21] pointed out that the commonest deformity of the knee in arthritis is flexion and sublaxation with outward rotation. This deformity presents a grave problem in the plan of reconstruction of the chronic arthritic patient as, no matter what procedures one may use—conservative stretching, manipulation or operation—only rarely is the knee a complete functional success. Flexion deformities can be prevented early in the disease and so simply that it can be done by any one. Swaim believed that if more care

19. Phemister, D. B.: Northwest Med. **27**:460 (Oct.) 1928.

20. Forkner, C. E.; Shands, A. R., and Poston, M. A.: Synovial Fluid in Chronic Arthritis, Arch. Int. Med. **42**:675 (Nov.) 1928.

21. Swaim, Loring T.: J. Bone & Joint Surg. **10**:742 (Oct.) 1928.

were exercised in the beginning of the active arthritis to foresee and prevent this one deformity, most patients with chronic arthritis would be on their feet much earlier than at the present time is possible. These deformities can be prevented by the use of properly applied plaster casts which should be bivalved and used at night and supplemented during the day with active exercise or a cuff with a heavy elastic band applied to the upper end of the tibia attached to a Balkan frame which takes away the mechanical force that causes the deformity.

MISCELLANEOUS

Fundamental Conceptions in the Understanding of Pathologic Change in the Bone.—Leriche and Policard [22] discussed the four fundamental principles which in their opinion must henceforth govern all investigations of pathologic change in the bone.

1. Bone tissue must be considered as a storehouse of mineral matters (subject to the fluctuations of the circulation). A large part of pathologic change in the bone must be regarded as resulting from anomalies or derangements of the mineral reserve function. In order to understand this it is essential to know by what physiologic process the mineral reserves that constitute bone are built up or torn down. The authors believe that variation in the blood supply plays a large part in causing withdrawal of calcium. By experiment, they have been able to demonstrate that increase of the circulatory activity in the region of a bone is followed by rarefaction of that bone, e. g., by ramisection or periarterial sympathectomy there is produced an intense vasodilatation with decalcification of the bone. Since active vasodilatation produces an excessive withdrawal of mineral matter from the bone, they conclude: (1) that active vasodilatation is the physiologic mechanism employed by the organism where it needs calcium; (2) that the organism when it needs mineral salts extracts them from the reserve supply by waves of vasodilating nerve impulses and (3) that all diseases either general or local which provoke active vasodilatation must cause decalcification of the bones in that region. They point to the phenomena of decalcification that are observed in pregnancy, in phosphate poisoning and after traumatisms as confirming these hypotheses. They also consider such lesions as Kienbock's disease, Kohler's disease and tarsal scaphoiditis as of vasomotor origin, characterized by a moderate rarefaction, spontaneously curable but with dysharmonic-osteogenic processes of repair.

2. The laws of osteogenic reconstruction in the adult govern anatomically the evolution of diseases of bone.

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22. Leriche, R., and Policard, A.: Presse méd. **36**:1282 (Oct. 10) 1928.

According to the authors, the fundamental principle is that at the beginning of every process of ossification there is produced an active hyperemia, acting simultaneously on the bone and on the adjacent soft tissues. This provokes a rarefaction of the former and an edema of the latter. The rarefaction sets free mineral salts, but as the ability of the blood to transport calcium is fixed at a constant, these salts become deposited in the adjacent soft tissues which have been prepared by the edema for participation in the reparative process. The same process applies to pathologic ossification whether resulting from infection or not.

3. Bone not only is a storehouse for minerals, but is also a hematopoietic organ.

According to the authors, the bone marrow has nothing to do with the phenomena of ossification or with the life process of bone. The reactions of bone and of the bone marrow are entirely independent.

4. The mechanism of growth in length of bone is purely of cartilaginous character.

The authors stated the belief that growth in length is bound up with a balance between two phenomena of inverse character which follow each other without ever stopping: the growth of cartilage and its destruction by the bone. If the cartilage cells cease to multiply, growth stops. If the cartilage fails to obtain nourishment, ossification does not take place and again growth stops. The cartilage is nourished by imbibition; its diseases are only trophic disturbances. Because of the absence of blood vessels, the cartilage is only affected by means of its exchanges even in infection and inflammation. Finally, the life and the death of the cartilage are regulated by endocrine influences. All diseases of growth of bone and the dystrophies of the epiphyseal cartilage ought to be studied in the light of these considerations.

[ED. NOTE.—Leriche and Pollicard have for a long time been profound students and active experimental investigators of the physiology of bone. The views expressed in the foregoing paragraphs represent a crystallization of ideas which have been previously expressed at greater length and more detail in book form. They support the physioclinical theory of ossification as contrasted with the osteoblastic cellular theory. While many of their ideas are purely speculative and their conclusions open to question, every one who is familiar with their work will admit its scholarly quality and its background of studious investigation and careful observation. All physicians who are interested in bone surgery should read their interesting and thought provoking book, The Physiology of Bone.[23]]

23. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems. Translated by Sherwood Moore and J. Albert Key, St. Louis, C. V. Mosby & Company, 1928, pp. 236.

Myofascitis.—Albee [24] defined myofascitis as a local manifestation of a general toxic condition, evidenced by a low-grade inflammation or toxic involvement of the muscles and fasciae, the symptoms predominating at the fascial insertions of muscle to bone. He has found it a prevalent condition and considers it a frequent cause of backache often misdiagnosed as sacro-iliac strain, lumbago, sciatica and muscular rheumatism. In his experience the evidence has indicated the colon as the source of the toxic absorption in 90 per cent of the patients, and the teeth, tonsils, sinuses, and gallbladder in the remaining 10 per cent. He has obtained striking relief of symptoms by removal of the toxic absorption from the colon, often in patients who had been entirely unrelieved by mechanical and supportive treatment of the spine.

[ED. NOTE.—Myofascitis as described by Albee may exist, but its presence is difficult to prove. Unfortunately, there is scarcely ever any chance of investigating the pathologic changes at necropsy. In cases such as these, it is almost impossible to rule out a mild toxic or infectious arthritis of the spine in a stage too early to show proliferative bone changes by roentgen examination. Measures susceptible of relieving the one ought also to benefit the other. Whether we call it myofascitis or arthritis, we can at least agree on the necessity of removing foci of infection and eliminating intestinal absorption in many cases of painful back.]

Volkmann's Ischemia.—Robert Jones' [25] clinical experience agrees with the experimental observations of Brooks and Jepson that venous obstruction is the chief causative factor in the production of Volkmann's ischemia. The pressure causing the obstruction may come from without (splints or bandages of a too flexed elbow) or from within (unreduced displacement of bones and subfascial hematoma). It is Jones' opinion that ischemic contracture might occur in spite of every precaution, but nevertheless the best treatment is prevention. The prophylactic measures which he advises and which have been successful in preventing the development of any instance of ischemia in his own practice are the following:

1. Reduction of dislocations and displaced bones as soon as possible. He does not advocate leaving unreduced a supracondylar fracture for several days in order to avoid ischemia. His method of reduction has been as follows: "I first extend the arm, supinating and pulling it at the same time. While the thumb is placed on the upper fragment the extended and stretched elbow should be flexed. This usually and without difficulty gives a complete reduction."

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24. Albee, Fred H.: Myofascitis from Orthopedic Standpoint, J. A. M. A. **91**:1364 (Nov. 3) 1928.

25. Jones, Robert: Brit. M. J. **2**:639 (Oct. 13) 1928.

2. Using no force in flexing the elbow. No force should be necessary; if the arm does not flex easily, it is suggestive of blocking due to displaced fragments.

3. Avoidance of circular compression.

4. Avoidance of all splints.

The wrist is slung in a collar and cuff sling under the chin. Whether or not there is swelling, it is a mistake to bandage the arm to the forearm or the elbow to the side.

5. For the first few days, critical observation of all fractures about the elbow.

For treatment of the fully developed condition, the author has for years used nothing but his own previously described method of gradual stretching, and he has often obtained good results by this method in patients who had been subjected to operation previously without success. In his experience, operative treatment has not been helpful; and he warns against bone resections, tenoplasties, myotomies and tenotomies.

[ED. NOTE.—Robert Jones first wrote on Volkmann's ischemic paralysis in 1908. Now, twenty years later, he has given his present views on the subject in a brief paper. No abstract can do justice to this paper, in which every conclusion and suggestion are based on a lifetime of experience.]

Bailey [26] stated that he has transplanted the internal epicondyle of the humerus by suturing it into a subperiosteal bed one third of the way down the shaft of the ulna for the relief of Volkmann's ischemia. Three weeks after the operation, the fingers could be completely extended. At the end of seven months, the patient had recovered almost perfect function in the limb. The operation was performed four months after the onset of the ischemia, which followed a supracondylar fracture. Massage and splintage had been tried in the interval, without any appreciable improvement.

Spontaneous Dislocations of Hip Joint During Early Life.—Hart [27] analyzed twenty-eight cases of spontaneous dislocation of the hip in children. He found that sixteen followed a metastatic septic arthritis, four were due to poliomyelitis, four to spastic paralysis and four resulted from tuberculosis and chronic arthritis. He considered that the essential factor in all cases is a muscular imbalance. Prevention is the best form of treatment, and to this end it is necessary to keep the hip from assuming the adducted, flexed and inwardly rotated position. Constant traction, if properly applied, is an effective therapeutic measure.

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26. Bailey, Hamilton: Brit. J. Surg. **16**:335 (Oct.) 1928.

27. Hart, V. L.: Spontaneous Dislocations of Hip Joint During Early Life, Arch. Surg. **17**:587 (Oct.) 1928.

"Riders' Leg."—Writing of "riders' leg," Winn [28] stated that he has encountered forty-two cases of this injury at the Cavalry school during the past two years. It is of great economic importance, being one of the chief causes of inability to ride among officers. "Riders' leg" is rare among enlisted men who use the McClennan type of saddle with long stirrups. The officers use a flat saddle with short stirrups. The cause is a severe strain of the adductor muscle group. The muscles involved are the pectineus, adductor brevis, adductor longus and adductor magnus. The author has never been able to demonstrate gross periosteal evulsion. The injury in all cases observed followed sudden exertion of the muscles due to an unexpected movement of the horse. The symptoms are sudden severe pain in the thigh, gradually becoming so severe that further riding is impossible. Pain recurs with attempted adduction or on walking with a long stride. Acute tenderness is found over the upper portion of the adductor longus. In some cases, ecchymosis is noticed in the pubic region. In most instances, recovery takes place in from a few days to two weeks. The injury, however, predisposes to further strains of the adductors. In recurrent cases, several months are sometimes required for recovery. Treatment consists in rest and the application of heat in mild cases. A diagonal cross hatched strapping with adhesive plaster from close up in the crotch to the midthigh gives immediate relief in mild cases. In old recurrent cases, the author uses an elastic thigh stocking.

SURGICAL PROCEDURES ON THE BONES, JOINTS AND TENDONS

Operative Lengthening of the Femur.—Abbott and Crego [29] described a method of lengthening the femur in patients with unilateral shortening of the leg which they have used successfully in eight patients. The same principle was employed as in their method of lengthening the tibia and fibula previously described. After performing a Z shaped osteotomy of the shaft of the femur and inserting transfixion pins in the upper and lower ends of the bone, an apparatus is applied which permits gradual distraction of the fragments while maintaining accurate alinement. By employing this apparatus, the authors were able to obtain an average increase in length of 2½ inches in four weeks. The lengthening finally obtained varied from 1½ to 3½ inches. There were no infections and no nonunions. The authors do not recommend this as a routine procedure, but advocate it in carefully selected cases.

[ED. NOTE.—Abbott and Crego's careful work and ingenious apparatus have made lengthening of the lower extremity a dependable procedure. About sixty patients have been operated on by them, with

28. Winn, D. F.: Mil. Surgeon **63**:507 (Oct.) 1928.

29. Abbott, L. C., and Crego, C. H.: South. M. J. **21**:823 (Oct.) 1928.

uniform success. There have been no disasters. At present, lengthening of the tibia and fibula is more of a standardized procedure and involves fewer difficulties than lengthening of the femur, but the latter method is still being developed.]

Results of Stabilizing Operation for Paralytic Hips.—Dickson [30] made a further report on the results obtained by the operative method previously described by him for stabilizing hips rendered unstable by paralysis of the gluteus maximus and minimus muscles. The operation consists in transplanting the origin of the tensor fasciae femoris from its position just external to the anterior superior spine to a new position on the crest of the ilium in the vicinity of the posterior superior spine, thus bringing the muscle posterior to the axis of the hip joint where it acts as an extensor instead of a flexor of the hip.

Dickson has operated on forty-six patients. Of these, thirty-two have been under observation a sufficiently long time to permit an estimation of the final result. In ten of these, the limp has been eliminated or greatly improved; in fourteen there has occurred a definite improvement in stability of the hip, but with a definite limp still remaining; in eight, the results have been failures in that no more improvement has been obtained than could have been expected by overcoming the hip-joint flexion deformity which was present. All the failures were in cases in which a weak or paralyzed tensor fasciae femoris muscle was used.

Operative Fusion for Tuberculosis of the Spine.—Henderson [31] discussed the rôle of fusion operations of the spine in Pott's disease, basing his remarks on a study of 301 patients on whom this operation in one of its various forms had been performed at the Mayo Clinic between 1912 and 1925. Albee's bone graft technic was employed in 269 patients and Hibbs' osteoplastic method in 32. In a few instances after the Albee method, secondary operations were required because of fracture of the graft. Only 16 of the patients operated on were under 10 years of age, and 227 of the patients were between 20 and 40 years of age.

It was found that the length of time necessary to complete the convalescence was nearer two years than one and sometimes more, and that the patients who were able to rest and observe the general antituberculous regimen improved much faster than those who did not. The author concluded that the operation has an important rôle in helping to obtain a cure and that it ought to be employed in adult patients who are in good general condition, and if there is no evidence of

30. Dickson, Frank D.: J. Bone & Joint Surg. **10**:712 (Oct.) 1928.

31. Henderson, M. S.: Operative Fusion for Tuberculosis of Spine, J. A. M. A. **92**:45 (Jan. 5) 1929.

impending wide dissemination of the disease and no draining sinuses to contaminate the operative field. He expressed the conviction that it is useless to subject to this operation patients who in addition to Pott's disease have advanced tuberculosis of the lungs or of the genito-urinary tract.

Extra-Articular Fusion of the Tuberculous Hip in Children.—Stating his conviction that patients with tuberculosis of the hip never recover a useful degree of motion, Kidner [32] advocated fusion of the hip by the extra-articular method. He considered this to be indicated even in the case of children. He has performed this operation in sixteen children and has followed them through to the end-result stage. In all cases, the progress of the disease has been arrested and symptoms relieved. He considers the juxta-articular methods of Kappis and Hibbs and the free graft method which he has devised preferable to the para-articular methods of Albee, Calvé and others. From this study he concluded that the earlier in the disease the operation is performed, the less will be the shortening and the shorter the period of invalidism.

[Ed. Note.—We have advocated arthrodesis for tuberculosis of the hip in adults for a number of years, but have been reluctant until recently to take the same stand in respect to children and to abandon all hope of recovery without ankylosis. Subsequent experience has, however, finally convinced us that to delay operation is to expose the child to serious risks and that ankylosis in good position is not only the best guarantee of cure, but also the best means of preserving maximum function.]

Recurrent Dislocation of the Shoulders.—Oudard [33] described a new operative procedure for the relief of recurring dislocation of the shoulder which in his hands has yielded satisfactory results. Its aim was to prevent the head from leaving the glenoid by the restraining influence of a bone block. Briefly, the operation consisted in exposing the front of the shoulder by turning back the anterior border of the deltoid, splitting the caracoid process in its long axis and detaching the outer half with its muscular insertions, and dividing the subscapularis muscle and the anterior portion of the capsule. The edges of the capsule and the subscapularis muscle were then overlapped and sutured in order to reef the relaxed structures. Finally, the detached portion of the coracoid was brought up into position and its base fixed by wire to the tip of the remaining portion. This resulted in the coracoid process being prolonged a distance of about 3 cm., sufficient for it to act as a bone block preventing the humeral head from displacing anteriorly.

32. Kidner, F. C.: End-Results of Extra-Articular Fixation of Tuberculous Hip in Children, J. A. M. A. **91**:1865 (Dec. 15) 1928.

33. Oudard: Presse méd. **36**:201 (Feb. 15) 1928.

[ED. NOTE.—It has been reliably stated that more than 150 different operative procedures have been devised for overcoming recurrent dislocation of the shoulder. Analysis of these different operations shows that with a few exceptions they fall into three groups: first, those dealing with the capsule and employing some method of strengthening it such as reefing, overlapping, etc.; second, those dealing with the humeral head and employing some adventitious tissue to hold it in place, fixation with fascia or tendon or transplantation of muscle, and, third, those which deal with the glenoid, aiming to prevent displacement by the introduction of a bone block. All of these methods have proved effective, and the criterion for selection should be simplicity as well as reliability. Fixation of the humeral head by the use of fascia or tendon seems to have a considerable advantage in this respect.]

Tendon Transplantation Technic.—In operations for the transplantation of tendons, Royle [34] recommended using the transplanted tendon as a living suture. He did this by splitting off strips from the transplanted tendon, threading them on fascial suture needles and weaving them in and out of the paralyzed tendon to which the transplant is to be secured.

FRACTURES

Fractures of Metatarsals and Phalanges.—Magnuson [35] found from his own experience that fractures of the metacarpals and phalanges were capable of producing disability far in excess of their apparent importance because of their effect on the function of the hand. Unless the fracture is properly reduced and the fragments maintained in correct alinement, the injury results almost uniformly in stiffness of the fingers and constitutes a serious handicap.

In fractures of the metacarpal bones, it is the pull of the interossei that has to be resisted with its tendency to cause a dorsal bowing or angulation of the fragments. In fractures of the middle phalanges of the fingers, the lumbricales muscles exert an extensor action on the distal fragments while the interossei tend to flex the proximal fragment causing the forward bowing deformity which presses against the flexor tendon of the finger.

[ED. NOTE.—Fractures of the phalanges and metacarpals are serious injuries and in our experience, yield a large degree of disability. The results are bad when the fractures are not properly reduced and are far from good even when anatomic reposition is obtained. Splinting should be reduced to a minimal period and motion started as early as possible if the results are to be improved.]

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34. Royle, N. D.: J. Coll. Surgeons, Australasia **1**:115 (July) 1928.

35. Magnuson, Paul B.: Fractures of Metacarpals and Phalanges, J. A. M. A. **91**:1339 (Nov. 3) 1928.

Compression Fractures of the Spine.—In a general survey of fractures of the spine, Osgood [36] found that compression fractures represent more than 50 per cent and that of these from 70 to 80 per cent involved the eleventh and twelfth dorsal or the first and second lumbar vertebrae. Most of them resulted from hyperflexion injuries. In untreated patients, one encounters the three stages of disability described by Kummell: first, the stage of initial injury; second, a period of comparative well being, and third, development of kyphos and pain. As far as diagnosis is concerned, the important thing is to suspect such an injury. Discussing the treatment in the different types of fracture, Osgood stated that fractures of the sacrum or coccyx usually respond to rest; that fractures of a single vertebra do well if the patient is treated in the recumbent position for from six to eight weeks with the aid of plaster jackets or hyperextension frames; that long standing cases, in which treatment has not been given, with persistent pain and deformity should be given the benefit of a fusion operation, which, however, should be preceded by a course of postural and corrective treatment.

Fractures of the Neck of the Femur in Childhood.—From a review of the literature, Colonna [37] concluded that fracture of the neck of the femur is an unusual injury in childhood. He reported six instances of this injury in children, the ages ranging from 5 to 16 years. The fractures were caused by severe violence. The symptoms were less severe than in adults, and there was only moderate disability. One of the patients was treated for a contusion of the knee for several weeks. Five of the fractures involved the cervicotrochanteric region, three being incomplete and two complete, and one was situated in the narrow portion of the neck. Five of the six patients were treated by a spica with the hip in abduction and one was treated with the hip in abduction in a Bryant frame. Three of the patients recovered with perfect function; in one, the limb was ⅛ inch shorter but no limp or limitation of motion was present. One, with an incomplete cervicotrochanteric fracture, showed 1¼ inches shortening and marked limitation of motion, but was able to get about without any apparatus, and the last had ¼ inch shortening with slight limitation in abduction.

DISLOCATIONS

Apparatus for Reduction of Fracture Dislocations of the Cervical Spine.—King [38] described a method of reduction for fracture dislocations of the cervical spine which have proved useful in his hands.

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36. Osgood, R. B.: New England J. Med. **199**:861 (Nov. 1) 1928.
37. Colonna, P. C.: Ann. Surg. **88**:902 (Nov.) 1928.
38. King, J. E. J.: Am. J. Surg. **5**:507 (Nov.) 1928.

A plaster cast was applied encircling the body, and in it was incorporated an apparatus consisting of two steel shoulder pieces mounted on which were two steel uprights terminating in a cross bar. A halter was fitted to the patient's head, and this in turn was connected with the cross bar. By means of a ratchet gear traction was exerted in the line of deformity until reduction was accomplished. This apparatus was worn for a period of six or eight weeks when a Thomas collar was applied.

Intra-Articular Dislocation of the Patella.—Jones [39] described an unusual injury to the patella in a boy, aged 11, following a fall. The patella was rotated 90 degrees so that the upper edge was directed backward and became wedged in the intercondylar notch of the femur. Manipulation under anesthesia failed to reduce the dislocation. At operation the knee joint was opened, and the bone forcibly levered back into position; it was then necessary only to suture the incision in the joint capsule made by the operator. The quadriceps extensor insertion had been stripped off the upper and anterior surfaces of the bone, but was not ruptured. Seven weeks after the accident, the knee joint was normal. Jones stated that fourteen similar cases have been described.

AMPUTATIONS

An Operation for Making the Forearm Prehensile after the Loss of a Hand.—Henry [40] succeeded in providing a patient whose left forearm had been amputated at the wrist with a prehensile extremity by splitting off a rod of bone from the outer side of the radius and enveloping this, together with the muscles in contact with it (flexor carpi ulnaris, flexor longus pollicis, radial wrist extensors, dorsal tendons of the thumb and the brachioradialis) and the radial artery, with skin. Active pronation of the forearm brought this newly formed digit into opposition with a fixed digit, supplied by means of a prosthesis. The patient was subsequently able to write with the left forearm. Henry expressed the belief that he could have dispensed with the prosthesis if he had partially fractured the ulna and bent it so as to give the newly formed digit a living opponent.

OSSIFICATION OF EXPERIMENTAL FRACTURES

Ossification After Fractures.—Ravdin and Morrison,[41] in a series of dogs, fractured the radius by open operation and studied the rate of ossification under various experimental conditions. The animals

39. Jones, Percy J.: Brit. J. Surg. **16**:338 (Oct.) 1928.

40. Henry, Arnold K.: Brit. J. Surg. **16**:188 (Oct.) 1928.

41. Ravdin, I. S., and Morrison, M. E.: Ossification After Fracture, Arch. Surg. **17**:813 (Nov.) 1928.

were divided into four groups: those in the first group were given 20 cc. of cod liver oil daily; those in the second group were given parathyroid extract Collip to raise the serum calcium level; those in the third group were subjected to thyroparathyroidectomy to lower the serum calcium level of the blood, and the animals in the fourth group were used as controls.

From their study of the results, they were inclined to minimize the effect on normal bone of a deficient inorganic phosphorus and calcium serum content. Union occurred in every instance with the exception of two hypocalcemic animals which did not live long enough for ossification to occur.

EFFECT ON THEIR FUNCTION OF STRETCHING NERVE TRUNKS

Tests on Sciatic Nerves.—By applying various amounts of tension to the sciatic nerve of a cat, Forbes [42] demonstrated that the power of conduction of an impulse is much impaired. Even the slight amount of tension necessary to dissect out the nerve is sufficient to affect its power of conduction considerably. Tension applied to a frog's nerve, however, has much less effect than in the mammal. The mammalian nerve undergoes a recovery period after stretching; presumably a nerve with intact blood supply would recover much more rapidly.

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42. Forbes, A.: New England J. Med. **199**:555 (Sept. 20) 1928

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